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GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

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New Drug Application for Obeticholic Acid (OCA)
for the Treatment of Primary Biliary Cirrhosis (PBC)
(New Drug Application [NDA] 207999)

Sponsor:

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ADVISORY COMMITTEE BRIEFING MATERIALS
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this report.

Abbreviation	Definition
6-ECDCA	6α-ethyl-chenodeoxycholic acid
α-SMA	α-stellate cell activation
AASLD	American Association for the Study of Liver Diseases
ADME	absorption, distribution, metabolism and elimination
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
ANCOVA	analysis of covariance
APRI	AST to platelet ratio index
ASBT	apical sodium-dependent bile acid transporter
AST	aspartate aminotransferase
BA	bioavailability
BAS	bile acid sequestrants
BCRP	breast cancer resistance protein
β-PDGF	β-platelet-derived growth factor
BE	bioequivalence
BSEP	bile salt export pump
CA	cholic acid
CDCA	chenodeoxycholic acid
CI	confidence interval
CK-18	cytokeratin-18
CL	confidence limit
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
CRP	c-reactive protein
CTX	cerebrotendinous xanthamatosis
CYP1A2	cytochrome P450 1A2
CYP2C9	cytochrome P450 2C9
CYP2C19	cytochrome P450 2C19
CYP2D6	cytochrome P450 2D6

Abbreviation	Definition
CYP3A	cytochrome P450 3A
CYP7A1	cholesterol 7α-hydroxylase
DB	double-blind
DSP	Dainippon Sumitomo Pharma
EASL	European Association for the Study of the Liver
EC_{50}	median effective concentration
EE	efficacy evaluable
ELF	enhanced liver fibrosis
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor-19
FGFR4	fibroblast growth factor receptor 4
FLINT	Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment
FXR	farnesoid X receptor
GGT	gamma-glutamyl transferase
glyco-OCA	glycine conjugate of OCA
HCC	hepatocellular carcinoma
HDLc	high-density lipoprotein cholesterol
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-6	interleukin-6
IL-12	interleukin-12
IL-23	interleukin-23
IND	Investigational New Drug
iNOS	inducible nitric oxide synthase
INR	international normalized ratio
IQR	interquartile range
ITT	intent-to-treat
kPa	kilopascals
LDLc	low-density lipoprotein cholesterol
LLN	lower limit of normal
LOCF	last observation carried forward
LPMCs	lamina propria mononuclear cells
LS	least square

Abbreviation	Definition
LTSE	long-term safety extension
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end stage liver disease
MMP-2	matrix metalloproteinase-2
MMRM	mixed-effect repeated measures
MOA	mechanism of action
NAFLD	non-alcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NDA	New Drug Application
NHS	National Health Services
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NTCP	sodium-taurocholate cotransporting polypeptide
OATP	organic anion transporting polypeptide
OATP1B1	organic anion transporter protein B1
OATP1B3	organic anion transporter protein B3
OCA	obeticholic acid
OST	organic solute transporter
OST-α/β	organic solute transporter alpha/beta
PBC	primary biliary cirrhosis (also called primary biliary cholangitis)
PBO	placebo
PD	pharmacodynamic
PDUFA	Pharmacy Drug User Fee Act
PK	pharmacokinetic
PRO	patient reported outcome
QD	once daily
QT	QT interval of the electrocardiogram
QTc	corrected measure between Q wave and T wave (in heart's electrical cycle)
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SCH	sandwich cultured hepatocytes
SE	standard error
SD	standard deviation

Abbreviation	Definition
SOC	System Organ Class
tauro-OCA	taurine conjugate of OCA
TE	transient elastography
TEAE	treatment-emergent adverse event
TGF-β	transforming growth factor-beta
TIMP-1	stellate cell apoptosis
TNF-α	tumor necrosis factor-alpha
UDCA	ursodeoxycholic acid
UK	United Kingdom
ULN	upper limit of normal
US	United States (of America)
VAS	visual analog scale
VSMCs	vascular endothelial cells

1. EXECUTIVE OVERVIEW

Intercept Pharmaceuticals, Inc. (Intercept) is seeking approval of obeticholic acid (OCA) for the treatment of primary biliary cirrhosis, recently named primary biliary cholangitis (PBC). This briefing document summarizes data included in the New Drug Application (NDA) submitted to the Food and Drug Administration (FDA) in support of this indication. Key information regarding the PBC disease landscape, current treatment options, and the clinical development of OCA to address the unmet medical need is summarized and discussed below and subsequently detailed in Section 2 through Section 8. **The Executive Overview has been cross referenced to the pertinent summary sections.**

Proposed Indication and Dosing Recommendations

The proposed indication for OCA use is based on the development of a safe and effective therapy for patients with PBC with an inadequate response to, or intolerant to, UDCA:

> *Obeticholic acid (OCA), a farnesoid X receptor (FXR) agonist, is indicated for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.*

The recommended starting dose is 5 mg once daily with titration to 10 mg once daily, as tolerated, to improve therapeutic response.

Disease Landscape

PBC is a rare chronic autoimmune liver disease that, in untreated patients, may progress to hepatic fibrosis, cirrhosis, hepatic decompensation, and death unless they receive a liver transplant (see Section 2). Since 1988, PBC has been the second leading cause of liver transplant in women in the United States. PBC disproportionately affects women versus men (approximately 10:1) and is typically diagnosed in patients between 40 years to 60 years of age.

Patients with PBC progress at varying rates (see Section 2.1). Some become decompensated over a period of several years while for others progression occurs over more than a decade. PBC is characterized by cholestasis caused by autoimmune destruction of biliary ductules with progressive impairment of bile flow in the liver. This results in increased hepatocellular bile acid concentrations which are toxic to the liver. Such hepatocellular injury is associated with a local inflammatory response resulting early on in an abnormal elevation of serum alkaline phosphatase (ALP) levels, a hallmark of the disease. PBC is often also heralded by the presence of anti-mitochondrial antibodies (AMA), observed in approximately 90% of patients. Patients can be diagnosed with probable PBC based on these two serum biomarkers. Liver biopsy, while confirmatory, is no longer the standard of care.

ALP is also routinely used to clinically monitor the disease and serves as a leading indicator of disease progression (see Section 2.2). With more advanced disease, hepatic excretory function starts to decline, leading to increased bilirubin, which therefore serves as a lagging indicator of disease progression. Two large clinical PBC databases with a combined total of more than 12,000 patients have independently confirmed a near log-linear correlation of both elevated ALP and bilirubin after 1 year of follow up with long-term liver transplant-free survival. Other commonly assayed serum liver enzymes such as gamma glutamyl transferase (GGT) and the

transaminases alanine aminotransferase (ALT) and aspartate aminotransferase (AST) also serve as markers of cholestatic and hepatocellular injury, respectively, as PBC advances.

The most common symptoms of PBC are fatigue and pruritus (see Section 2.3). The mechanisms underlying these symptoms are not well elucidated and neither of them correlates with disease stage or clinical outcomes. Fatigue is reported in up to 78% of patients with PBC and no effective therapies have been described to date. The incidence and severity of pruritus vary widely within the patient population and there are a number of therapeutic options available to manage it. Pruritus may subside spontaneously when patients progress to cirrhosis and hepatic decompensation, suggesting a pruritogen that is synthesized in the liver.

Other manifestations of PBC include hyperlipidemia and osteoporosis observed at all stages of the disease (see Section 2.4). In advanced decompensated disease, typical complications of cirrhosis and decompensation occur (eg, esophageal varices and bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy and HCC), all of which are associated with decreased survival in PBC patients (see Section 2.5).

Treatment Landscape

Ursodeoxycholic acid (UDCA), an epimer of the primary human bile acid chenodeoxycholic acid (CDCA), is the only medicine currently approved to treat PBC (see Section 2.6). It has been shown to improve ALP and bilirubin and to delay histological progression, thereby increasing liver transplant-free survival. Accordingly, UDCA treatment has been recommended as first line therapy for patients with PBC in the treatment guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL). While UDCA has had a marked impact on clinical outcomes in PBC, ALP remains abnormally elevated in 70% of patients taking a therapeutic dose of UDCA.

The risk of adverse outcomes associated with inadequate or no response to UDCA (as determined primarily by ALP and, in more advanced disease, bilirubin as well) is substantial. This is significantly more common in patients who are younger at disease onset, presumably reflecting a more aggressive disease course. In a recent study, 50% of patients who had presented with PBC under the age of 50 were either non-responsive to UDCA with resulting increased risk of liver transplant or death or had already undergone liver transplant.

Liver transplant can significantly improve survival in PBC; however, it is a high-risk procedure and suitable only for patients with advanced liver disease. Many patients experience a poor quality of life after liver transplant and transplant recipients often demonstrate poor functional outcomes (eg, only 10% of recipients return to work or notice improvement in quality of life). Furthermore, due to the underlying autoimmunity that characterizes the disease, PBC recurs in a significant percentage of transplanted patients.

While research has been conducted on a number of other drugs (eg, azathioprine, methotrexate, colchicine, D-penicillamine, cyclosporin A, chlorambucil, fibrates, and glucocorticosteroids), little to no evidence supports the benefit of these compounds.

Development History

OCA is a selective and potent agonist of the farnesoid X receptor (FXR), a dedicated bile acid receptor expressed primarily in the liver and small intestine. CDCA is the natural endogenous ligand for FXR. OCA is derived from CDCA by the chemical addition of a single ethyl in the 6-carbon position of the molecule (ie, 6α-ethyl-CDCA), resulting in an approximately 100-fold more potent FXR agonist than CDCA, which permits low therapeutic dosing. Activation of FXR regulates bile acid homeostasis enterohepatically, as well as inflammation and fibrosis in response to liver injury. OCA therefore represents a novel therapy for PBC, possessing a mechanism of action complementary to that of UDCA which has no FXR activity.

The OCA clinical development program in PBC was comprehensive, particularly in light of the rarity of the disease (see Section 3). This involved a careful evaluation of the clinical pharmacology of OCA as well as clinical efficacy and safety studies characterizing the effect of OCA (see Section 4). The program includes 17 Phase 1 and Phase 2 clinical pharmacology studies; 2 double-blind, placebo-controlled, 3-month Phase 2 studies (747-201 and 747-202); one double-blind, placebo-controlled, 12-month Phase 3 study (747-301); and 3 open-label, long-term safety extension (LTSE) phases for the Phase 2 and 3 studies.

In the Phase 2 studies (see Section 5.1), once daily, oral treatment with OCA at doses ranging from 10 mg to 50 mg resulted in superior reduction of ALP (primary endpoint) and other biomarkers reflecting improved liver function compared with placebo when administered either as monotherapy and in combination with UDCA. The 10 mg OCA dose demonstrated equivalent efficacy to the higher doses with better tolerability, which informed the choice of doses in the subsequent Phase 3 study.

In the Phase 3 study (see Section 5.2), patients were randomized (1:1:1) to receive once daily placebo, OCA 10 mg, or OCA titration (5 mg to 10 mg). The majority (93%) of patients received treatment in combination with UDCA and a small number (7%) of patients unable to tolerate UDCA received OCA as monotherapy. The primary endpoint of the study was the proportion of patients achieving a composite of ALP <1.67x ULN (with a ≥15% reduction) and bilirubin ≤ULN).

The key Phase 3 study results are as follows:

- Treatment with OCA 10 mg or OCA titration (5 mg to 10 mg) for 12 months resulted in 47% and 46% of patients achieving the primary composite endpoint, respectively, as compared to 10% of patients in the placebo group (both OCA groups p<0.0001). Therapeutic response to OCA was demonstrated at all time-points across the 12-month treatment period (p <0.0001 versus placebo).
- The majority (77%) of patients from both OCA groups combined achieved a reduction of at least 15% in ALP at 12 months compared to 29% of patients on placebo. In addition, 36% of patients treated with placebo experienced an increase in ALP compared to 3% of OCA-treated patients.
- Mean total bilirubin levels increased in the placebo group and were maintained in the OCA treatment groups, suggestive of a slowing of disease progression with OCA.
- ALP and bilirubin responses were maintained during continued OCA treatment assessed at 2 years in the open-label LTSE; placebo patients crossed over to OCA treatment in the

LTSE exhibited improvements in both ALP and bilirubin after 1 year of therapy, consistent with the levels achieved by the OCA groups during the double-blind phase.

- Similar OCA treatment results to the overall study population were observed in subgroups of high risk patients known to have reduced transplant free survival, including males, younger patients (<50 years), patients with ALP >3x ULN, and patients with advanced disease.
- OCA treatment resulted in significant improvements in secondary endpoints associated with liver damage secondary to cholestasis (eg, GGT, ALT and AST), as well as exploratory markers of immune status and inflammation (eg, IgM and CRP). An evaluation of transient elastography that was available in a smaller subset of patients indicated that progression of fibrosis was significantly attenuated in the OCA 10 mg group compared with placebo.
- The incidence of clinical outcomes associated with PBC disease progression in the Phase 3 study was expected to be low since most patients were earlier in disease stage and given the relatively short duration of the study. Using retrospectively defined criteria including mortality and liver related outcomes, a total of 3 (4%) placebo-treated patients had 5 clinical outcomes and 3 (2%) OCA-treated patients had 4 clinical outcomes.

The safety of treatment with OCA was characterized in over 430 patients with PBC. This included 155 patients with at least 2 years of exposure, and 14 patients with at least 5 years of exposure for a total of 675 patient years of OCA exposure (see Section 6).

Fatigue and pruritus are common symptoms of PBC. In the Phase 2 and Phase 3 studies, up to approximately 37% of patients had a medical history of fatigue and up to approximately 50% of patients had a history of pruritus. While treatment emergent fatigue was reported more frequently in the Phase 3 study as an adverse event (AE) in the OCA groups than in the placebo group, there was no difference between groups as assessed by the patient reported fatigue outcomes tool (PBC-40) and no patients discontinued due to fatigue.

Pruritus was the most frequently observed adverse drug reaction in OCA-treated patients. It was mild or moderate in most patients with a dose-related incidence. In the Phase 3 study, patient reported pruritus scores (eg, the visual analog score) demonstrated that the patient experience of pruritus improved over time. In the Phase 2 studies, pruritus resulted in significant rates of discontinuation, particularly at the 50 mg dose. However, employing the titration approach in the Phase 3 study (5mg titrating to 10mg) significantly mitigated both the incidence and severity of pruritus, resulting in only a single patient discontinuation in the OCA titration group over 12 months of treatment. With the exception of pruritus, the rates of common AEs observed with OCA treatment were generally similar across different treatment groups.

PBC is also characterized by hyperlipidemia, particularly high HDL–C levels that exceed LDL-C levels. Treatment with OCA in the Phase 3 study was associated with an early and sustained small decrease in HDL-C levels; these levels remained within the normal range with long-term treatment. Small and transient increases were observed in LDL-C levels at Week 2 in OCA-treated patients. However, levels returned to baseline over the course of the study and were similar to placebo by the end of treatment.

A small number of OCA-treated PBC patients in the Phase 3 study experienced hepatic-related adverse events and elevations in liver biochemistries. The nature of these events was consistent with those reported in patients with advanced chronic liver disease. Overall and across the

pooled Phase 2 and 3 studies, the incidence of adverse hepatic reactions were similar in the placebo, OCA 10mg and OCA titration groups (<1%, <1% and 0%, respectively).

Long-term treatment with OCA was not associated with any changes in the overall safety profile of the drug. As in the double-blind phase, the most commonly reported AE was pruritus.

Taken together, these data support an overall favorable benefit-risk profile of OCA therapy in combination with UDCA for the treatment of PBC in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

Regulatory History

The FDA has granted OCA Orphan Drug designation, Fast Track designation, and Priority review. Due to the rarity of PBC and its slowly progressive natural history, it is difficult to conduct studies assessing hard clinical endpoints in this patient population. As a result, an AASLD convened group of PBC experts has recommended the use of surrogate biochemical endpoints to assess investigational new therapies for PBC. The Sponsor's clinical development plan was accordingly established to consider approval of OCA in the treatment of PBC based on surrogate biochemical endpoints under accelerated approval guidelines.

Accelerated approval is available to drugs intended to treat a serious, life-threatening disease based on a surrogate endpoint "reasonably likely to predict clinical benefit". The determination that a surrogate endpoint meets this requirement is a matter of judgement based on the entirety of clinical evidence including correlation with clinical outcomes and relationship to disease pathophysiology.

The Phase 2 and Phase 3 studies of OCA in patients with PBC were designed with primary endpoints based on ALP alone and as a composite with bilirubin, respectively. The use of these biomarkers for accelerated approval is supported by their relationship to PBC pathophysiology and clinical studies conducted by other companies and academic institutions across the globe. These include independent single center studies which were followed by the more robust Global PBC Study Group (>6100 patients) and the UK-PBC Research Cohort (>5900 patients) clinical databases. All of these studies have independently and reproducibly demonstrated that ALP and bilirubin, alone and in combination, are strongly correlated with liver transplant-free survival (see Section 2.7). As such, these data provide evidence to establish the validity of the composite endpoint as "reasonably likely to predict clinical benefit" in patients with PBC.

The Sponsor is committed to confirming the clinical benefit of OCA in a large controlled Phase 3b clinical outcomes study in patients with advanced PBC in accordance with accelerated approval regulatory requirements (see Section 3). This study is a global, randomized, placebo and historical-controlled study of patients with PBC at elevated risk for complications (as defined by the bilirubin > ULN to ≤ 3x ULN or ALP >5x ULN). The primary objective is to evaluate the effect of OCA on a composite of mortality and liver related outcomes. The study was initiated in December 2014 and is actively enrolling patients, targeting 170 sites globally and expected to be completed on a post-marketing basis.

2. OVERVIEW OF PBC

Primary biliary cirrhosis/cholangitis (PBC) is a rare chronic liver disease that, if left untreated, typically progresses to hepatic fibrosis, cirrhosis, hepatic decompensation, and death unless a patient receives a liver transplant.

PBC is a rare, serious, life-threatening autoimmune liver disease characterized by cholestasis with progressive impairment of bile flow in the liver that results in increased hepatocellular bile acid concentrations that are toxic to the liver. Such toxicity results in a local inflammatory response and is signaled early on by the secretion of alkaline phosphatase (ALP). In patients with an inadequate response to ursodeoxycholic acid (UDCA) therapy, the disease frequently progresses to hepatic fibrosis and eventual cirrhosis, hepatic decompensation, and death unless a patient receives a liver transplant (Kuiper 2010).

PBC disproportionately affects women versus men (approximately 10:1) and is typically diagnosed in patients between 40 to 60 years of age. It is estimated that 1 in 1000 women over the age of 40 are affected. Recent data suggest that those who are younger at onset (diagnosed before 50 years of age) or male have a worse prognosis (Carbone 2013). Racial or ethnic differences in patients with PBC have not been consistently identified (Al-Harthy 2012, Boonstra 2012).

Based on well-defined and rigorous case ascertainments, the incidence and prevalence rates for PBC in Europe, North America, Asia, and Australia are reported as ranging from 0.33 to 5.8 per 100,000 inhabitants and 1.91 to 40.2 per 100,000 inhabitants, respectively (Boonstra 2012). Kim et al estimated that there were 47,000 prevalent cases of PBC in the United States white population and that approximately 3500 new cases are diagnosed each year (Kim 2000).

PBC is considered to be an autoimmune disease, and while the cause of the disease is unclear, genetic predispositions have been described (Pratt 2005, Hirschfield 2009, Mells 2011). It is believed that the disease may be triggered by a response to a number of factors, such as infection or chemical exposure, followed by a chronic autoimmune response. Concomitant autoimmune diseases, particularly Sjögren's disease, sicca syndrome and scleroderma, are common (Kumagi 2008)

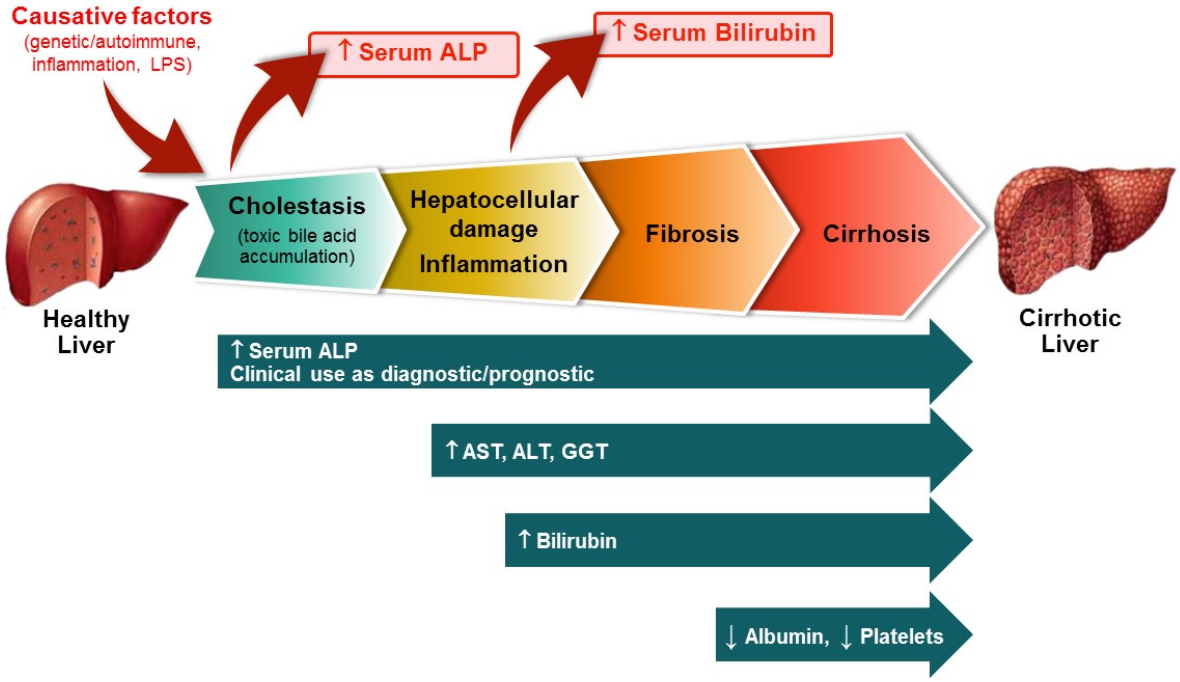
2.1. Natural History

Over 60% of the newly diagnosed cases are asymptomatic. The majority of asymptomatic patients become symptomatic within 10 years and the estimates for developing symptoms at 5 and 20 years are 50% and 95%, respectively (Kumagi 2008). As shown in Figure 1 liver function begins to deteriorate in patients with PBC prior to the onset of symptoms. The median time to progression from a positive AMA test to persistently abnormal liver enzymes was 5.6 years (range 1 to 20 years; Al-Harty 2012).

ALP increases with disease progression, as does bilirubin in more advanced disease, and both are highly predictive of long-term clinical outcomes, eg, transplant-free survival (Beuers 2011, Lammers 2014, Lammers 2015, Carbone 2013). An estimated average time from first appearance of AMA to death is approximately 20 years to 22 years without treatment (Mayo 2008). It should be noted that disease progression can vary significantly, with some

patients progressing to decompensation over a period of years and others remaining asymptomatic for more than a decade (Al-Harty 2012, Selmi 2011). Ultimately, the conjoint effects of chronic cholestasis and bile-duct destruction lead to progressive liver impairment culminating in liver failure resulting in liver transplant or death.

Figure 1: Schematic Representation of the Natural History of PBC



ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; PBC = primary biliary cirrhosis/cholangitis

2.2. Biochemical, Immunological, and Other Non-Invasive Markers of PBC

Progressive increases in ALP and, subsequently, bilirubin are reflective of the underlying hepatic disease pathology in PBC patients.

Antimitochondial antibody (AMA) and immunoglobulin M (IgM) are specific immunological hallmarks of PBC, and AMA is a diagnostic marker of the disease in approximately 90% of patients (Hirschfield 2013). ALP is the primary predictive and reliable marker of PBC progression. Patients with elevated ALP are at increased risk of histological progression, cirrhosis, hepatocellular carcinoma (HCC), and transplant. Bilirubin is also a marker of hepatic degradative function and becomes elevated in more advanced PBC. As PBC advances, the transaminases alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may also be elevated due to hepatocellular damage secondary to cholestasis. While gamma-glutamyl transferase (GGT) lacks specificity, elevation of this enzyme in the presence of elevated ALP is confirmatory of a cholestatic condition such as PBC (Giannini 2005).

Cholestatic liver disease is associated with profound inflammation. Markers of inflammation and apoptosis that may be evident include C-reactive protein (CRP; Pepys 2003), tumor necrosis factor (TNF; Hirschfield 2013), and cytokeratin-18 (CK-18; Feldstein 2009).

There are several imaging-and biomarker-based non-invasive fibrosis assessments that may be utilized in PBC. These include transient elastography (TE; Corpechot 2012) used to measure liver stiffness as an assessment of liver fibrosis stage and enhanced liver fibrosis (ELF; Lichtinghagen 2013), a composite serum biomarker score that has been correlated with fibrosis stage in chronic liver disease.

2.3. Symptoms of PBC

Pruritus and fatigue are the most common symptoms of PBC; however, they do not correlate with disease stage or clinical outcomes.

Pruritus and fatigue are the most common symptoms reported by patients with PBC (Mayo 2008, Crosignani 2008); however, they do not correlate with disease severity or clinical outcomes. Neither the specific pruritogen nor the underlying mechanisms for cholestatic pruritus have been elucidated, although the autotaxin pathway has been implicated (Beuers 2014).
A population-based study of PBC patients in England found that the cumulative risk for developing pruritus in a subset of previously asymptomatic patients at 1, 5 and 10 years was 13%, 31% and 47% respectively (Mayo 2008). However, pruritus incidence and severity are unpredictable from patient to patient over the course of the disease and may subside spontaneously when patients decompensate and develop hepatic failure, suggesting the pruritogen is synthesized in the liver (Jones 1999, Jones 2012). There is a well-defined treatment paradigm for cholestatic pruritus: addition of antihistamines or bile acid binding resins such as cholestyramine, are first-line therapy, followed by rifampicin and, in more intractable severe cases, biliary drainage can be an effective intervention.

Fatigue is reported in up to 78% of patients. While effective treatments exist for pruritus, no effective therapies for fatigue have been described to date.

2.4. Other Manifestations of PBC

Other manifestations of PBC include hyperlipidemia and osteoporosis observed at all stages of the disease.

Lipid abnormalities, including triglycerides, low-density lipoprotein cholesterol (LDLc), and high-density lipoprotein cholesterol (HDLc), are observed at all stages of the disease, but significantly, elevated HDLc is frequently observed early. Studies have generally shown that hyperlipidemia in patients with PBC is not associated with an increased risk of cardiovascular disease (Crippin 1992, Longo 2002, Allocca 2006, Ungprasert 2014).

Osteoporosis occurs in up to one-third of patients for reasons that are not well understood. Patients with PBC appear to have “low-turnover” osteoporosis in which bone formation is inhibited and bone resorption is low or low to normal (Adorini 2009). Vitamin D metabolism is normal in patients with PBC except for those with jaundice and clinically advanced disease

(Lindor 2009). As is common with autoimmune diseases, many patients also have other concomitant autoimmune diseases.

2.5. Clinical Outcomes of PBC

Clinical complications of PBC, such as varices, ascites, hepatic encephalopathy, and HCC are all associated with decreased survival in patients.

The course of PBC, like other chronic liver diseases, may last several decades, and the natural disease course has been estimated to average 20 to 22 years from onset to death without treatment (Mayo 2008).

As the liver is progressively damaged, liver cirrhosis, liver failure, and the complications of hepatic decompensation can ensue. All the typical complications of cirrhosis and decompensation (esophageal varices and bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and HCC) are observed. Many of these complications develop secondary to portal hypertension, which has a poor prognosis. In contrast to other liver diseases, portal hypertension may develop in pre-cirrhotic patients with PBC (Crosignani 2008, Lindor 2009).

2.6. Treatment Landscape in PBC

There is a clear ongoing unmet medical need for second-line therapies for patients with this serious, life-threatening disease.

The current management paradigm for patients with PBC is limited. UDCA, an epimer of the primary human bile acid chenodeoxycholic acid (CDCA), is the only drug approved for the treatment of PBC in the United States (US) or Europe. Its use is widespread and recommended in both US (AASLD; Lindor 2009) and European (EASL 2009) treatment guidelines. Liver transplant is a salvage option for late diagnosis and failed response to UDCA.

UDCA

Up to 70% of patients who are currently being treated or are intolerant to UDCA have an elevated ALP (Lammers 2014).

UDCA improves ALP and bilirubin and delays histological progression (Poupon 1997, Corpechot 2008). The results of clinical studies with appropriate dosing of UDCA and duration of treatment, together with well-controlled epidemiologic analyses, provide strong evidence that treatment with UDCA increases liver transplant-free survival, with significantly greater benefit for patients with significant biochemical responses as measured primarily by decreases in ALP and maintenance of normal bilirubin levels. An analysis by the Cochrane group (Rudic 2012) has challenged these findings. However, this meta-analysis included multiple studies of insufficient duration and sub-therapeutic doses of UDCA and has been rejected by both AASLD and EASL in their guidelines for the treatment of PBC (Lindor 2009, EASL 2009).

A large proportion of patients have an inadequate response, and ALP remains elevated in up to 70% of patients who are currently being treated or are intolerant to UDCA (Lammers 2014). Such patients remain at risk of disease progression and longer term clinical outcomes.

Liver Transplant

Liver transplant can significantly improve survival; however, as a salvage therapy, it is far from optimal and not available to all patients with PBC associated end stage liver disease.

Despite near universal use of UDCA, 10%, 22% and 44% of UDCA-treated patients progress to liver transplant or death over 5, 10, and 15 years (Lammers 2014). Liver transplant is an invasive and expensive procedure suitable only for patients with advanced end-stage liver disease. Complications of liver transplant include perioperative and surgical complications, bleeding, rejection, infection, and side effects from medications such as immunosuppressants. Unfortunately, many patients experience a poor quality of life after liver transplant, especially fatigue, which is unaffected by liver transplant (Pells 2013). In addition, recipients of liver transplants often demonstrate poor functional outcomes. Furthermore, the disease recurs in a significant percentage of patients post-transplant (Silveira 2010, Lindor 2009).

Other Potential Therapies

While research has been conducted on a number of other therapies (azathioprine, methotrexate, colchicine, D-penicillamine, cyclosporin A, chlorambucil, fibrates, glucocorticosteroids), these studies have not supported the benefit of any of these compounds (Lindor 2009, Rudic 2012).

2.7. Clinical Utility of Biochemical Markers for the Management of PBC

Biochemical response criteria are predictive of clinical outcomes. Despite the use of varying methodologies, small cohort analyses consistently associated lower ALP and/or bilirubin with improved prognosis.

Several centers have published studies describing the utility of biochemical markers to identify patients at greater risk for clinical outcomes (Pares 2006, Corpechot 2008, Corpechot 2011, Kumagi 2010a, Kumagi 2010b, Kuiper 2009).

Both the Global PBC Study Group and the UK-PBC Research Cohort databases have further supported ALP and bilirubin as biochemical response criteria.

Intercept sponsored the efforts of both the Global PBC Study Group and UK-PBC Research Cohort. These are independent academically run initiatives and the company was not involved in study design, data collection, analysis, or publication. Intercept has collaborated with both groups to confirm that ALP and bilirubin can be used as acceptable surrogate endpoints to support regulatory approval. Their large size and patient-level data minimize the shortcomings inherent in analyses of smaller cohorts.

Both databases have yielded new insights in PBC including: (1) the identification of novel susceptible gene loci for PBC (Mells 2011); (2) sex and age as determinants of UDCA responsiveness (Carbone 2013); (3) the impact of PBC on quality of life (Mells 2013); (4) the impact of liver transplant on systemic symptoms associated with PBC (Pells 2013); (5) the consideration of ALP and bilirubin as continuous variables when applied as biochemical endpoints of outcomes (Lammers 2014); and (6) the stratification of HCC risk in PBC (Trivedi 2015).

2.7.1. Global PBC Study Group and UK-PBC Research Cohort: Relationship Between Biochemical Markers and Clinical Outcomes

The Global PBC Study Group is an international multicenter collaboration between 15 liver centers in 8 North American and European countries with pooled clinical data from a retrospective database of 6191 patients with PBC.

The Global PBC Study Group database (Lammers 2014) includes long-term follow-up (>10 years in most patients; 7.3 years median follow-up) and detailed patient-level information (baseline clinical characteristics, longitudinal liver biochemistries, and long-term outcomes) and spans a broad range of patient demographics and other characteristics that may influence disease course (disease stage, age, gender, and regional differences in standard of care). This is a contemporary dataset with diagnosis established after 1990 for 79% of patients, while the median year of diagnosis was 1998 (interquartile range [IQR] 1991 to 2004).

The UK-PBC Cohort is a database of individual patient data in >5900 patients with PBC living in the UK.

Data collection for the UK-PBC Research Cohort began in 2007 and was established initially to undertake UK-PBC genome-wide association studies. Since 2008, the project has been on the portfolio of the National Institute for Health Research Comprehensive Research Network and works with the PBC Foundation to recruit patients via the UK-PBC Consortium, a research network consisting of 150 National Health Service (NHS) Trusts throughout the UK that is estimated to have captured approximately 25% of the PBC population in the country.

2.7.1.1. Transplant-Free Survival Rates with UDCA Use

Both the Global PBC Study Group and UK-PBC Research Cohort databases clearly demonstrate the value of UDCA therapy on liver transplant-free survival (Table 1), but there remains an unmet medical need in patients with PBC in the UDCA era.

Table 1: Transplant-Free Survival Rates in the UK-PBC Research Cohort and Global PBC Study Group

	Transplant-Free Survival Rates in Patients with PBC					
	UK-PBC Research Cohort (% Survival)			Global PBC Study Group (% Survival)		
	5 years	10 years	15 years	5 years	10 years	15 years
Total Cohort	94	84	76	88	77	63
UDCA-treated	96	88	82	90	78	66
Untreated	85	70	58	79	59	32

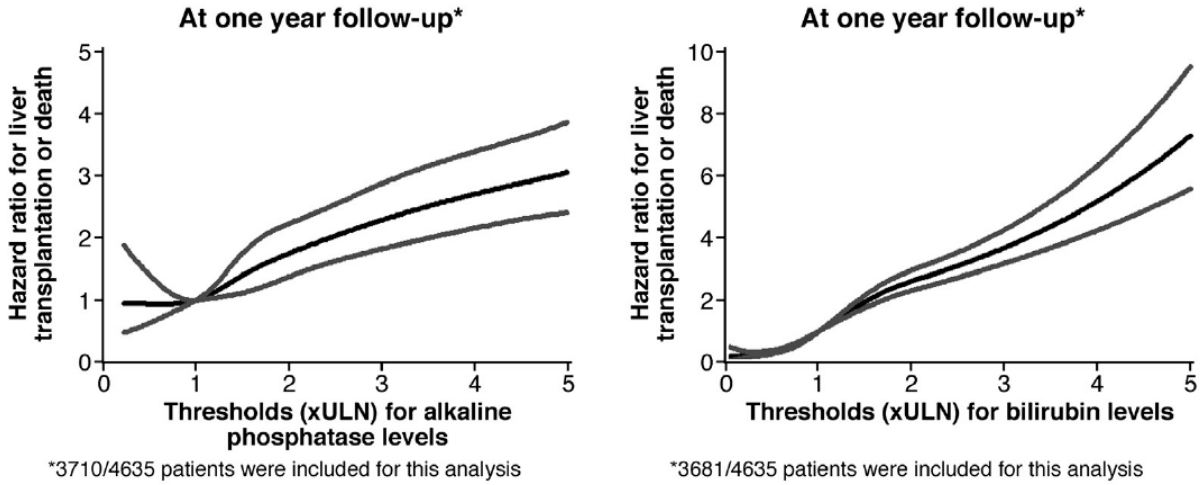
PBC = primary biliary cirrhosis; UDCA = ursodeoxycholic acid
For the UK-PBC Research Cohort, transplant-free survival is based on the occurrence of liver transplant or liver-related death.
For the Global PBC Study Group, transplant-free survival is based on the occurrence of liver transplant and all-cause mortality.

2.7.1.2. Association with Clinical Outcomes

The Global PBC Study Group database demonstrates a continuous and near log linear relationship between ALP and bilirubin levels and clinical outcomes (liver transplant and/or all-cause mortality), regardless of treatment.

As shown in Figure 2, a continuous and near log linear relationship was observed between ALP and bilirubin levels and clinical outcomes (Lammers 2014). These data confirm the association of ALP and clinical outcomes, consistent with the use of ALP to diagnose and manage the disease and monitor treatment effectiveness.

Figure 2: Higher ALP and Bilirubin Values are Associated with Higher Hazard of Liver Transplant and/or Death (Global PBC Study Group)



Hazard ratios are represented by the dark black line and 95% confidence interval by the gray line.

Importantly, when ALP values are considered together with bilirubin, the predictive value is enhanced in both datasets. Notably, the additional utility of ALP was observed in patients with

both normal and abnormal bilirubin. This finding was also evident in relevant patient subgroups, including untreated patients (Lammers 2014).

2.7.2. Assessment of Response Criteria Used in the Phase 3 Clinical Study (747-301)

The primary endpoint for the Phase 3 pivotal study (747-301) was the proportion of patients achieving specific biochemical criteria for ALP and bilirubin (ALP <1.67x ULN [with a ≥15% reduction] and bilirubin ≤ULN).

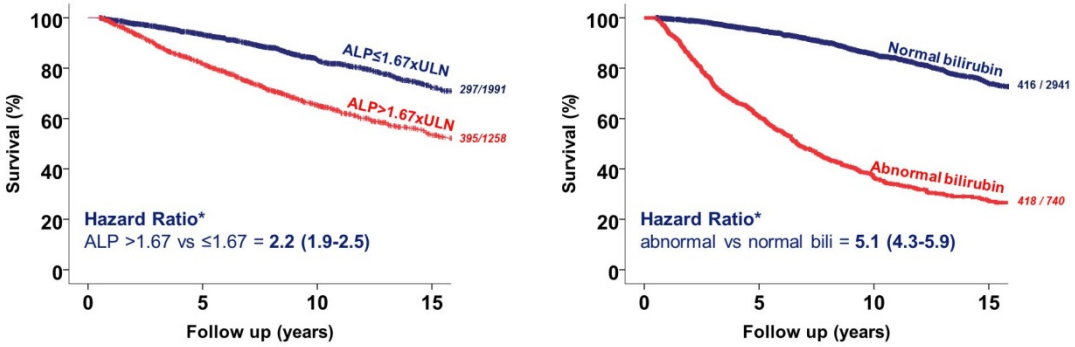
At the time of the design of the Phase 3 clinical study, ALP <1.67x ULN after 1 year of follow-up was shown to be predictive of histological progression of PBC, both alone and in combination with bilirubin, (Kumagi 2010a, Momah 2012). The minimum 15% reduction in ALP was included in the composite to ensure that patients who initiated the study with an ALP close to the 1.67 cutoff had a clinically meaningful ALP response in order to be considered to have met the primary endpoint. Bilirubin has long been a well-established independent predictor of prognosis across multiple chronic liver diseases. It is incorporated in risk models commonly used in clinical practice, such as Child-Pugh, MELD and Mayo PBC risk score. In fact, doubling of bilirubin was the regulatory endpoint used to support initial approval of UDCA in the US.

The availability of the Global PBC Study Group and UK-PBC Research Cohort allowed for independent validation of the Phase 3 composite endpoint and its association with clinical outcomes in patients with PBC.

The evaluations of the Phase 3 endpoint described in this section will focus on results from the Global PBC Study Group, which were confirmed in the UK-PBC Research Cohort.

As assessed in the Global PBC Study Group database, Cox regression analysis confirmed that the ALP threshold of 1.67x ULN assessed after 1 year of follow-up was highly predictive of liver transplant-free survival (Figure 3). As expected, abnormal bilirubin was also associated with worse prognosis for abnormal versus normal bilirubin (Figure 3).

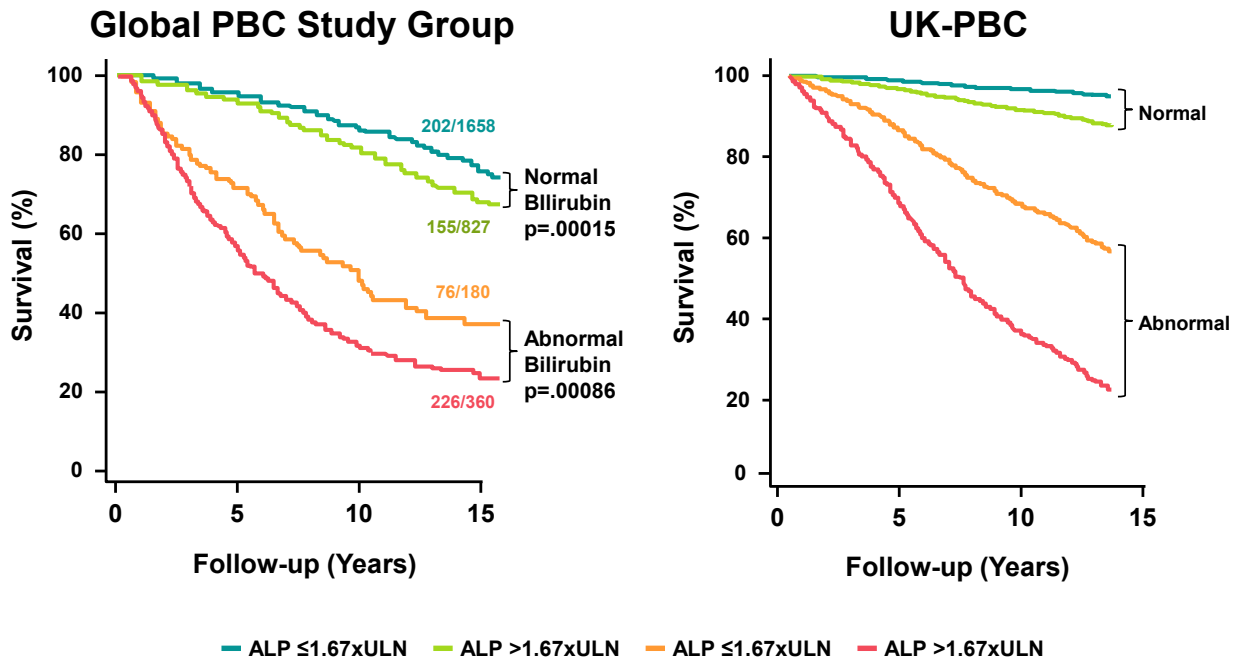
Figure 3: ALP >1.67x ULN and Abnormal Bilirubin Values at 1 Year of Follow-Up Were Associated with a Worse Prognosis in Patients with PBC (Global PBC Study Group)



ALP = alkaline phosphatase; PBC= primary biliary cirrhosis; ULN = upper limit of normal; Survival = liver transplant-free survival
*Adjusted for: center, gender, age, year of diagnosis

Importantly, the ALP cutoff 1.67x ULN added additional prognostic utlility for transplant-free survival when combined with bilirubin in both the Global PBC Study Group and UK-PBC Research Cohort databases (Figure 4). The risk of patients with normal bilirubin values and ALP values >1.67x ULN was higher compared with patients with normal bilirubin and ALP values ≤1.67x ULN. In the group of patients with abnormal bilirubin, the risk was also higher for patients with ALP values >1.67x ULN than ≤1.67x ULN.

Figure 4: ALP Values Have Predictive Significance in Addition to Bilirubin in Patients with PBC (Global PBC Study Group and UK-PBC Research Cohort)



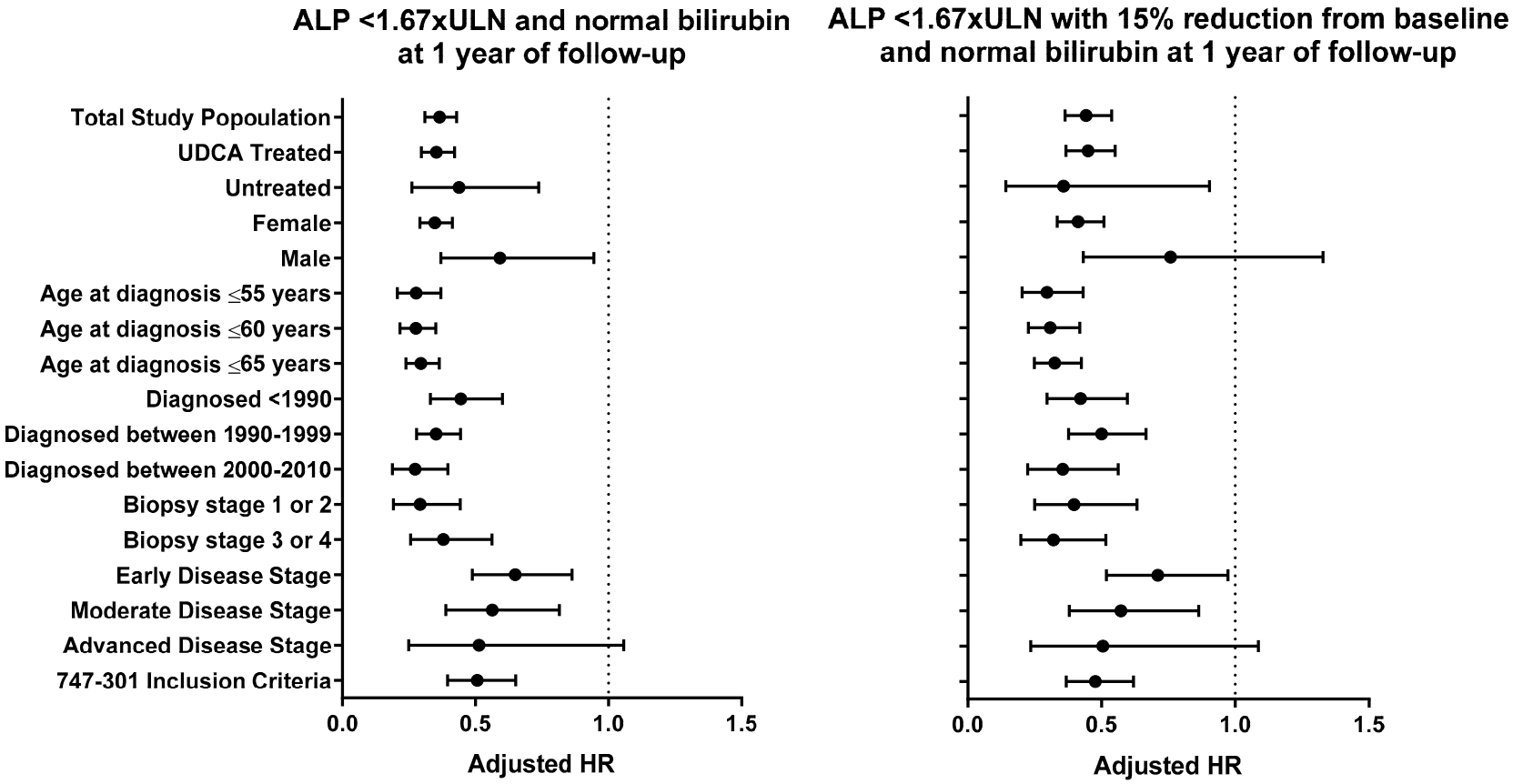
ALP = alkaline phosphatase; PBC= primary biliary cirrhosis; ULN = upper limit of normal; Survival for Global PBC Study Group = all-cause mortality; Survival for UK-PBC Research Cohort = liver-related mortality

Consistent with findings from the Global PBC Study Group and UK-PBC Research Cohort, the prognostic value of the Phase 3 primary composite endpoint is associated with improved prognosis.

The Study 747-301 primary composite endpoint at 1 year of follow-up (with and without the 15% reduction in ALP component) was further evaluated in a number of pre-specified subgroups (Figure 5). In nearly all subgroups, including untreated patients, achieving the composite endpoint was associated with improved prognosis.

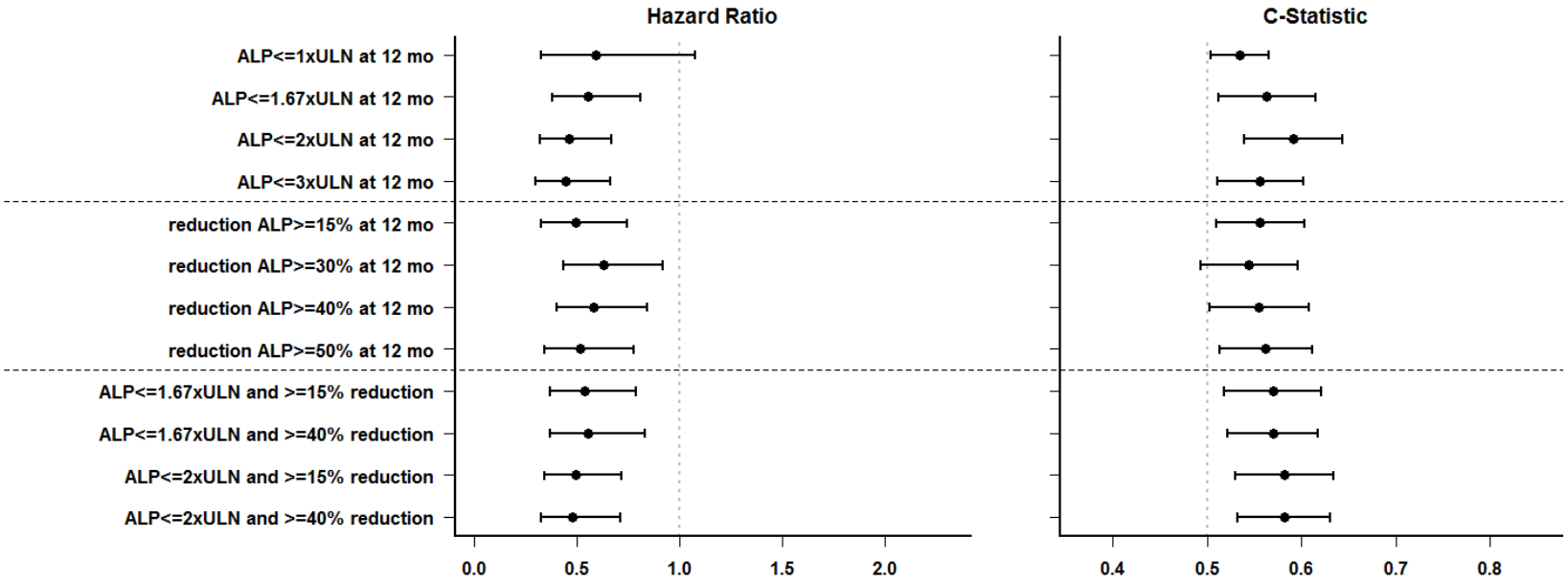
Further evaluation of varying ALP thresholds and percent reductions were conducted using the Global PBC Study Group database, specifically in those patients who would have met the Study 747-301 inclusion criteria. Consistent with the nature of the association between ALP and outcomes described by Lammers et al., hazard ratios for ALP thresholds ranging from 1x to 3xULN, percent reductions in ALP ranging from 15% to 50% and combinations thereof were all associated with lower point estimates for transplant-free survival with achievement of the indicated goal (Figure 6).

Figure 5: Adjusted Hazard Ratio for Composite Endpoint of ALP <1.67x ULN and a Normal Bilirubin at One Year of Follow Up for Total Study Population and Specified Subpopulations- Liver Transplant-Free Survival (Global PBC Study Group Database)



ALP = alkaline phosphatase; HR = hazard ratio; UDCA = ursodeoxycholic acid
Unpublished data from the Global PBC Study Group based on a personal communication from B. E. Hansen

Figure 6: Hazard Ratios (±95% CI) and C-statistics (±95% CI) for Risk of Liver Transplant or Death by ALP Thresholds and Percent Reductions in ALP in Global PBC Study Group Patients who met 747-301 ALP Inclusion Criteria and Were Treated with UDCA



Unpublished data from the Global PBC Study Group based on a personal communication from B. E. Hansen

In summary, the prognosis for patients diagnosed with PBC is extremely poor and current treatment options for patients with PBC are limited. Patients who are inadequate responders to, or intolerant of, UDCA experience more rapid disease progression and are at significantly greater risk of long-term adverse clinical outcomes.

The rarity of disease coupled with slow disease progression makes studies with hard clinical endpoints difficult.

The understanding of the surrogate relationship of ALP and bilirubin to PBC disease state and prognosis has been advanced by the availability of large cohort data from the Global PBC Study Group and UK-PBC Research Cohort, which have both confirmed near log linear relationships of ALP and bilirubin elevations with outcomes.

Collaboration with these groups has led to confirmation that the Study 747-301 primary composite endpoint is predictive of liver transplant-free survival in the overall PBC patient population and across a number of relevant subgroups. Importantly, these subgroups included untreated patients and those who met the Study 747-301 entry criteria. The former suggests that the relationship of the endpoint with outcomes is associated with the disease state and is not specific to UDCA, while the latter indicates that the endpoint is relevant to the Phase 3 study population. As such, these data support the use of the composite endpoint to evaluate the efficacy of OCA as a proposed treatment in PBC.

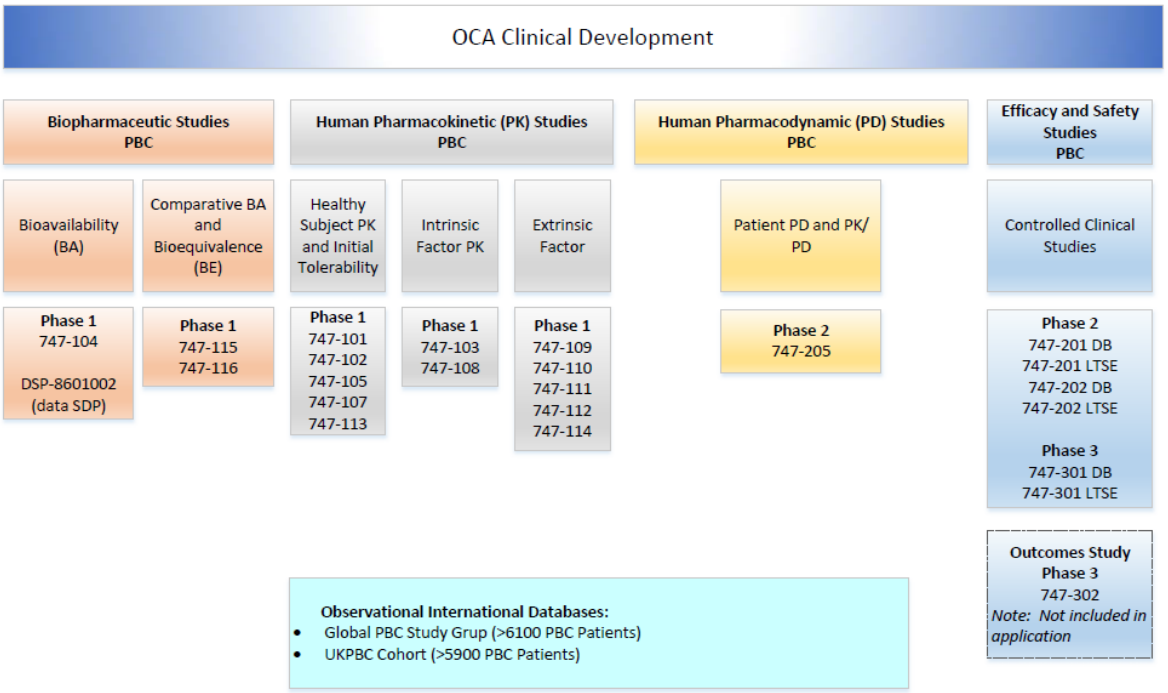
3. CLINICAL DEVELOPMENT OVERVIEW

The OCA clinical development program in PBC was comprehensive, particularly in light of the rarity of the disease. Clinical studies included a careful evaluation of the clinical pharmacology of OCA as well as clinical efficacy and safety studies characterizing the effect of OCA.

The clinical development program for OCA for the treatment of PBC is comprised of 17 clinical pharmacology studies; 2 double-blind, placebo-controlled, 3-month Phase 2 studies; one double-blind, placebo-controlled Phase 3 study; and the open-label, long-term safety extension (LTSE) phases for the Phase 2 and 3 studies (Figure 7). Long-term safety data has been collected out to over 5 years in the open-label LTSE studies.

Patients enrolled in the 3 double-blind, placebo-controlled PBC studies were representative of the target population for the proposed indication. This included patients who were suboptimally controlled on maximum recommended daily doses of UDCA. Although the majority of the target population is expected to receive OCA as a second-line therapy added to UDCA, a small subset of PBC patients are unable to tolerate UDCA and will be candidates for OCA monotherapy. In the Phase 3, pivotal study, patients with advanced disease (defined in Section 5.2.3) demonstrated a similar proportion of OCA-treated patients achieving the primary composite endpoint compared to OCA-treated patients with non-advanced disease stage. Results of these analyses would indicate similar efficacy regardless of disease progression.

Figure 7: OCA Clinical Development Program



OCA has also been studied in other indications (Intercept Sponsored and Investigator Initiated) which are not included in the table.
DB = double-blind; LTSE = long-term safety extension; NAFLD = Nonalcoholic Fatty Liver Disease; PBC = Primary Biliary Cirrhosis; DSP = Dainippon Sumitomo Pharma
NASH = Nonalcoholic Steatohepatitis

The Phase 3b confirmatory clinical outcomes Study 747-302 was initiated in December 2014 in accordance with the FDA's accelerated approval guidelines. The study is a global, randomized, placebo-and historical-controlled study including patients with PBC at elevated risk for complications (as defined by the biochemical criteria of bilirubin > upper limit of normal (ULN) to ≤ 3x ULN and/or ALP >5x ULN). This confirmatory study will assess a composite endpoint of clinical outcomes. Using the Global PBC Study Group data, an approximate 50% event rate (composite of mortality and liver-related outcomes) in this population over the course of approximately 8 years is predicted.

The primary objective of this confirmatory study is to evaluate the effect of OCA on a composite of mortality and liver-related outcomes when administered to patients with PBC. The liver related outcomes include:

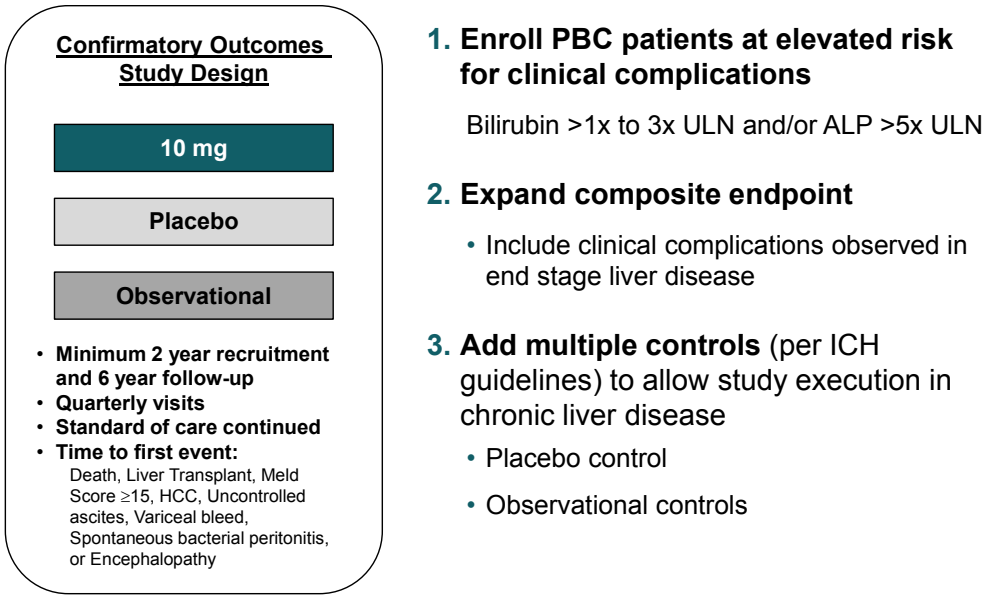
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of 2 or greater)

- Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (therapeutic paracentesis for diuretic-resistant ascites) at a frequency of at least twice in a month

There are potential patient recruitment and retention challenges to conduct a placebo-controlled study in this rare disease population. Therefore, the study design incorporates several factors to create a balance between feasibility and scientific integrity (Figure 8). These include:

1) Inclusion of PBC patients at elevated risk for clinical complications so that clinical outcomes may be measured in a reasonable timeframe.
2) An expanded composite endpoint, which includes hard endpoints of liver transplant or death typically evaluated in a confirmatory clinical study, as well as clinical complications associated with PBC.
3) The use of both placebo and observational (matched) controls to allow study execution in a rare disease.

Figure 8: Confirmatory Outcomes Study Design Balances Feasibility and Scientific Integrity



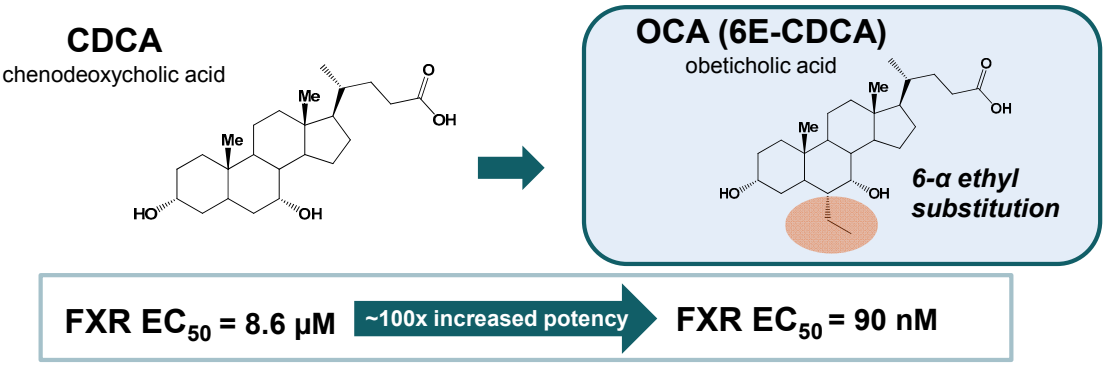
In addition to the placebo control group, the confirmatory study includes (1) a pre-specified key secondary analysis comparing clinical outcomes in the OCA treatment arm to historical controls and (2) a backup primary analysis comparing all patients treated with OCA to all control patients, ie, randomized placebo and historical controls in the event that enrollment or retention of patients in the placebo group meets pre-specified criteria. The study is currently enrolling patients with advanced PBC in multiple countries and is expected to be completed on a post-marketing basis to confirm OCA's clinical benefit in PBC.

4. CLINICAL PHARMACOLOGY OF OBETICHOLIC ACID

OCA is structurally similar to the endogenous bile acid chenodeoxycholic acid (CDCA) with the addition of an ethyl group in the 6-alpha position (6α-ethyl-CDCA), which makes it a 100-fold more potent FXR agonist.

OCA is a FXR agonist and modified bile acid. OCA is structurally similar to CDCA except for an additional ethyl group in the 6-alpha position. OCA retains many of the physicochemical and pharmacokinetic (PK) properties of CDCA, but is an approximately 100-fold more potent FXR agonist compared to CDCA, its natural endogenous ligand in the bile pool (Figure 9).

Figure 9: Obeticholic Acid is a Potent Farnesoid X Receptor Agonist



EC_{50} = median effective concentration

Similar to endogenous bile acids, OCA is extensively conjugated to the dietary derived amino acids glycine and taurine in the liver to form glyco-OCA and tauro-OCA, respectively. The glycine and taurine conjugates of OCA are approximately equipotent on FXR. Since OCA and its conjugated forms have similar potency on FXR, exposures levels of OCA are summarized as total OCA (ie, the sum of OCA, glyco-OCA, and tauro-OCA) for simplicity.

4.1. Mechanism of Action

OCA exerts its effects in PBC through its FXR-mediated regulation of bile acid homeostasis and anti-inflammatory and anti-fibrotic effects in the liver.

The primary mechanism of action of OCA in the treatment of PBC is improved bile acid homeostasis, together with anti-inflammatory and anti-fibrotic activity in the liver. As an FXR agonist and modified bile acid, an understanding of OCA's pharmacodynamic effects and potential benefits in the treatment of PBC warrants a brief overview of FXR pharmacology and bile acid physiology.

4.1.1. Bile Acid Physiology

Bile acids are synthetized in the liver and undergo efficient enterohepatic circulation; OCA, a semi-synthetic bile acid, exhibits similar metabolic and enterohepatic cycling as endogenous bile acids.

Bile acids are amphipathic, detergent-like molecules synthesized in the liver from cholesterol by multiple enzymatic steps. In humans, newly-synthesized bile acids (termed primary bile acids) consist of chenodeoxycholic acid (CDCA) and cholic acid (CA). Cholesterol 7α-hydroxylase (CYP7A1) is the rate-limiting enzyme in the synthesis of both primary bile acids. Before active secretion into the canalicular lumen, primary bile acids are conjugated with the dietary amino acids taurine or glycine, rendering the conjugated bile acid impermeable to membranes and less cytotoxic (Hofmann 2008).

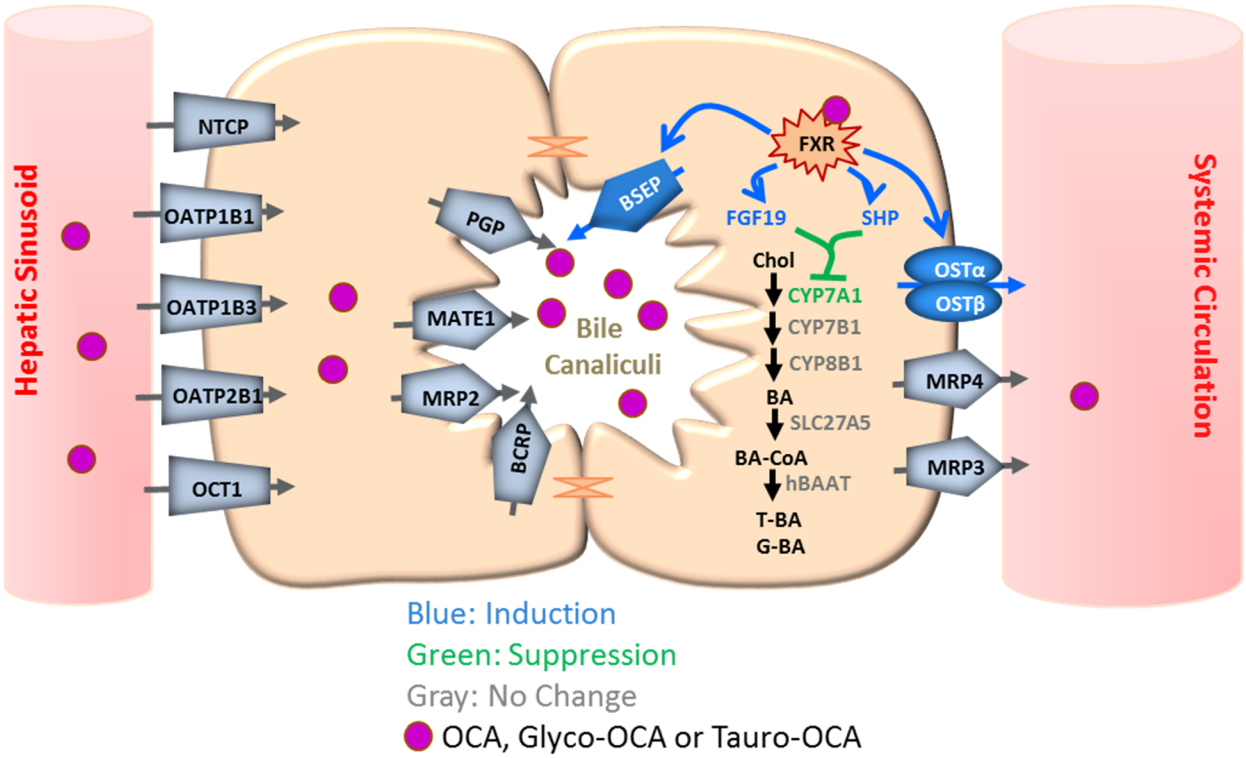
After food ingestion, bile acids are released from the gall bladder into the duodenum to promote the absorption of dietary lipids and lipid-soluble vitamins. Thereafter, conjugated bile acids travel to the distal ileum for active absorption and then return to the liver via the portal vein, to be re-secreted into the bile (Love 1998).

Transporter proteins play a critical role in maintaining the enterohepatic circulation and bile acid homeostasis (Thomas 2008). The enterohepatic circulation of bile acids involves transporter-mediated processes (Dawson 2009, Klaassen 2010) presented in Figure 10.

In the ileum, activation of FXR leads to the secretion of enterokine fibroblast growth factor-19 (FGF-19) that ultimately acts upon fibroblast growth factor receptor 4 (FGFR4) receptors expressed on the cell surface of hepatocytes causing the down-regulation of CYP7A1. FXR activation in the hepatocytes also causes induction of proteins involved in the transport of bile acids out of the liver including bile salt export pump (BSEP) and organic solute transporter alpha/beta (OSTα/β) (Figure 10).

FXR activation leads to decreased bile acid synthesis and increased bile acid secretion from the liver, which is ideal for treating cholestatic liver diseases including PBC.

Figure 10: Transporter and Metabolizing Enzymes Involved in Liver Bile Acid Homeostasis

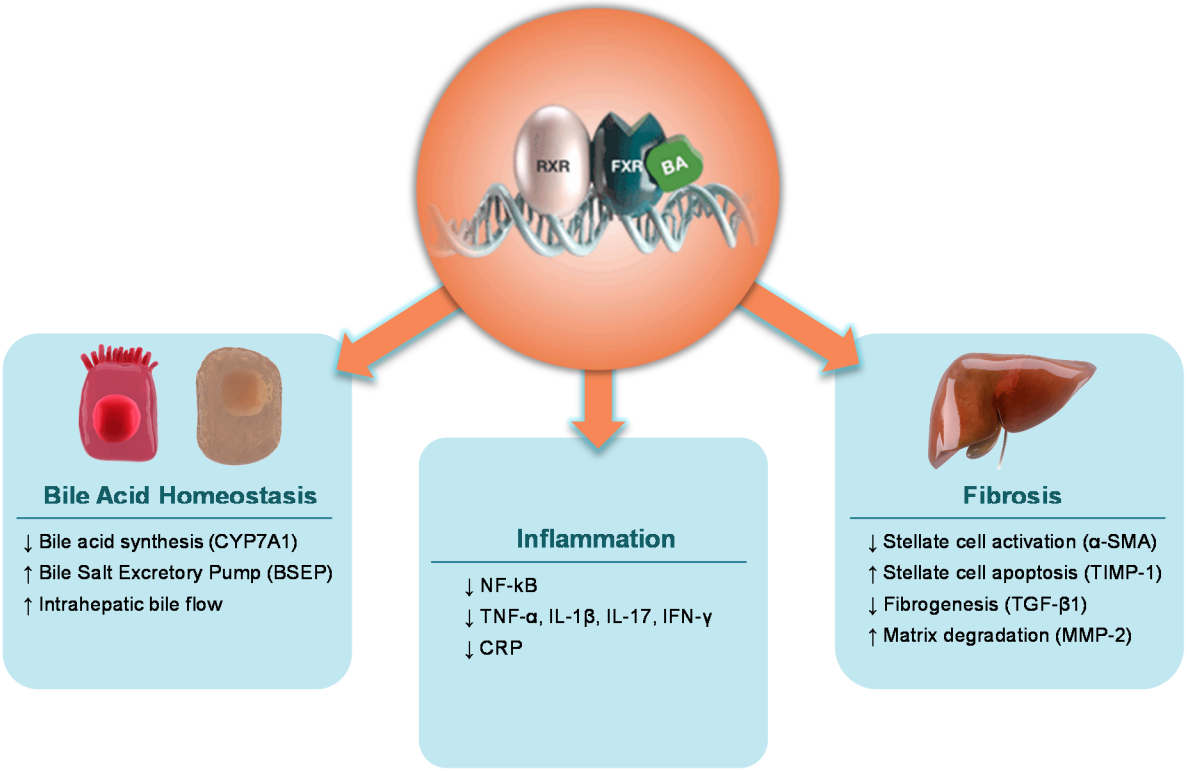


4.1.2. Farnesoid X Receptor (FXR) and Bile Acid Homeostasis

Nuclear receptors constitute a family of ligand-activated transcription factors which, once activated, modulates a number of receptor-specific target genes. FXR is a dedicated nuclear receptor for bile acids and represents an attractive target for the treatment of chronic liver diseases (Figure 11).

FXR is a nuclear receptor expressed at high levels in the liver and intestine. Nuclear receptors constitute a family of ligand-activated transcription factors, which can either activate or repress target genes. Similar to other nuclear receptors, FXR works in concert with other transcription factors and coactivators to down regulate the expression of CYP7A1, the enzyme that catalyzes the rate-limiting step of bile acid synthesis. Activation of FXR not only inhibits bile acid synthesis from cholesterol but, importantly, protects against the toxic accumulation of bile acids through decreased hepatocyte uptake of bile acids, increased basolateral efflux into the sinusoidal spaces, as well as increased apical secretion. These mechanisms limit the overall size of the circulating bile acid pool while promoting choleresis, therefore limiting hepatic exposure to bile acids. Therefore, as a bile acid sensor, FXR regulates bile acid homeostasis and this mechanism underlies the primary therapeutic rationale for FXR agonists in cholestatic liver diseases such as PBC, where FXR targeting can protect the liver from the development of fibrosis and cirrhosis through these and other mechanisms (Modica 2012).

Figure 11: FXR Mechanism of Action in Cholestatic Liver Disease



4.1.3. FXR and Inflammation

OCA activation of FXR has anti-inflammatory effects in hepatic and extra-hepatic cells.

OCA pharmacodynamic effects also include the ability to exert anti-inflammatory effects as demonstrated across a variety of *in vitro* and *in vivo* models. Direct anti-inflammatory effects were demonstrated in hepatocyte cell models with notable improvements in inflammatory markers such as tumor necrosis factor-alpha (TNF-α) mRNA levels, COX-2 induction, and TNF-α stimulated inducible nitric oxide synthase (iNOS) production. These effects were extended to extra-hepatic *in vitro* models including atherosclerosis (vascular endothelial cells [VSMCs]) and intestinal disease (lamina propria mononuclear cells [LPMCs] from colonic and ileal biopsies obtained from individuals with irritable bowel disease).

4.1.4. Fibrosis and FXR

OCA activation of FXR has direct anti-fibrotic effects in multiple animal models of chronic liver, intestinal and renal diseases.

Anti-fibrotic effects have been demonstrated across numerous *in vitro* and *in vivo* models. Evidence for the direct anti-fibrotic effect of OCA activation of FXR was obtained using

immortalized human stellate cells, which become activated in chronic liver diseases and propagate fibrogenesis. OCA treatment significantly inhibited progression of fibrosis and reversed established fibrosis and cirrhosis in the thioacetamide model of liver fibrosis in rats. These effects were coupled with a trend toward decreased fibrotic marker mRNA in the liver (αSMC, TGF-β1 receptor, β-platelet-derived growth factor [β-PDGF] receptor, and collagen I) and an additional effect to reduce portal hypertension in OCA-treated rats (Albanis 2005). Similar anti-fibrotic effects were noted with: (1) hepatic injury induced by exposure to high fat diet (Vignozzi 2011), (2) urinary bladder injury induced by exposure to high-fat diet (OCA treatment in Western diet fed rabbits: Morelli 2012), (3) nephropathy induced in mice on a high-fat diet (Wang 2009) and, (4) nephropathy associated with chemically induced type 1 diabetes (Wang 2010).

4.2. Comparison of OCA to UDCA and Other Bile Acids

OCA and UDCA have distinct mechanisms of action that complement each other in the treatment of PBC.

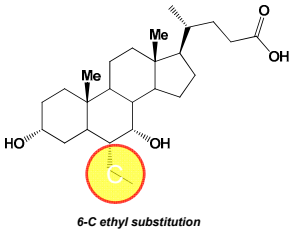
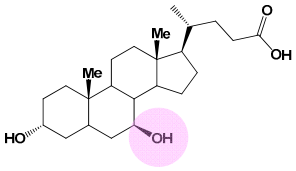
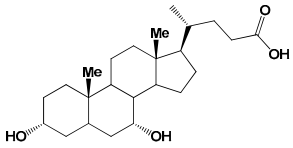
UDCA elicits its effects in PBC by:

- Protection of cholangiocytes against cytotoxicity of hydrophobic bile acids
- Stimulation of hepatobiliary secretion
- Protection of hepatocytes against bile acid–induced apoptosis

The primary activity of OCA is attributable to its activity on FXR and downstream effects to decrease bile acid synthesis, regulate of transporters to favor choleresis, and includes anti-inflammatory and anti-fibrotic mechanisms, as discussed above. UDCA has no meaningful FXR activity and therefore OCA provides a complementary mechanism of action in the treatment of PBC. UDCA's primary mechanism involves increasing the hydrophilicity of the endogenous bile acid pool to render it less cytotoxic. To achieve this dilution, UDCA is administered at a therapeutic dose range of 13 mg/kg/day to 15 mg/kg/day. In contrast, because OCA is a potent FXR agonist, it can be dosed at only 0.07 to 0.14 mg/kg/day.

The description of bile acid signaling pathways via FXR has led to the development of OCA for the treatment of patients with PBC. While OCA is derived from CDCA, and UDCA is its natural epimer, the small structural differences between these molecules confer distinct pharmacological profiles and corresponding mechanisms of action (Table 2).

Table 2: OCA has Distinct Mechanism of Action Compared to Other Bile Acids

	OCA	UDCA	CDCA
Structure			
Status	Investigational	Marketed	Marketed
Indication	PBC	PBC, Cholesterol Gallstone Dissolution	Cholesterol Gallstone Dissolution Cerebrotendinous Xanthamatosis (CTX)
Dose Required for Therapeutic Effect	0.07 mg/kg/day	13 to 15 mg/kg/day	13 to 16 mg/kg/day
FXR Activation (EC_{50})	0.090 µM	None	8.66 µM
MOA	Specific FXR-mediated control of gene transcription resulting in the inhibition of bile acid synthesis and transport of bile acids out of the liver	Hydrophilicity of UDCA results in decreased cytotoxicity of circulating bile acids.	Suppresses hepatic synthesis of both cholesterol and cholic acid
Effect on Bile Acid Pool	Reduction in bile acid pool	Dilutes toxic concentrations of hydrophobic bile acids	Displaces cholic acid and its metabolite deoxycholic acid in an expanded bile acid pool

CDCA = chenodeoxycholic acid; EC50 = median effective concentration; FXR = farnesoid X receptor; MOA = mechanism of action; OCA = obeticholic acid; UDCA = ursodeoxycholic acid

4.3. Pharmacokinetic Properties of OCA

The pharmacokinetic (PK) properties of OCA are similar to CDCA and are characterized by extensive enterohepatic recirculation.

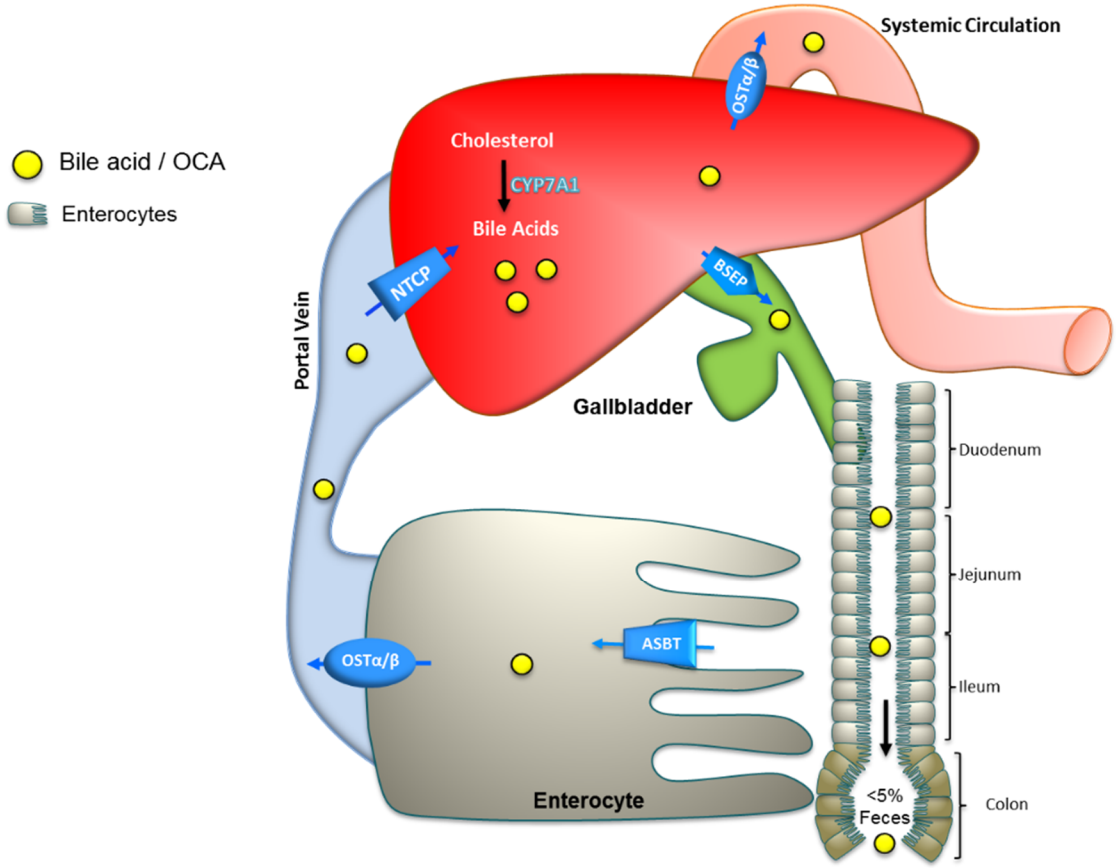
The PK profiles of OCA have been investigated in healthy subjects, PBC patients, and patients with hepatic impairment. OCA is rapidly absorbed with peak concentrations (C_{max}) occurring approximately 2 hours after dosing. OCA is extensively taken up by the liver where it is immediately conjugated to amino acids glycine and taurine, consistent with CDCA (Figure 12). The conjugates of OCA are then primarily secreted into bile where they are sequestered in the gallbladder and discharged to the duodenum after a meal. The conjugates of OCA are reabsorbed in the terminal ileum and recirculated in the liver or excreted in feces, the principal route of elimination.

A result of the extensive enterohepatic recirculation is that OCA and its conjugates primarily reside within the liver and intestine and only 17% of OCA is systemically bioavailable.

In addition, there is significant accumulation of glyco-OCA, and tauro-OCA which have pharmacological activity equal to the parent drug.

Exposure of total OCA generally increased dose proportionally with steady-state concentrations achieved within 9 days after daily administration. Exposure of OCA was, on average, less than 20% of the steady-state concentration 2 weeks after cessation of dosing. Upon administration of radiolabeled OCA, more than 85% is excreted in feces. Urinary excretion is minimal (less than 3%).

Figure 12: OCA and Bile Acid Enterohepatic Circulation



Modestly higher systemic exposure of total OCA was observed in patients with PBC relative to healthy subjects consistent with changes in the uptake and elimination characteristics in patients with cholestasis.

4.4. Effect of Intrinsic Factors on Pharmacokinetics

4.4.1. Demographic and Baseline Characteristics

A pooled population PK analysis was conducted using data from 16 studies including healthy volunteers, PBC patients, and special populations (hepatic impairment). The effects of weight,

age, sex, and disease state on OCA PK were assessed. Results from the analyses indicate that the demographic factors of age and sex do not have clinically meaningful effects on the PK of OCA and no dose adjustment is needed.

When evaluating the effect of disease status (PBC patients versus non-PBC patients) on PK, the plasma exposure of OCA was higher in PBC patients than non PBC patients at steady-state.

4.4.2. Hepatic Impairment

Higher systemic exposures and, to a lesser extent, higher liver exposures of OCA are expected in patients with moderate and severe hepatic impairment. Based on data from population PK modeling and simulations, a modified dosing regimen of OCA is recommended in patients with moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C).

The effects of hepatic impairment on PK and safety of OCA were assessed in a Phase 1 study (747-103) and in patients with portal hypertension (747-204).

In Study 747-103, systemic (plasma) exposure levels of endogenous bile acids were significantly higher in patients with moderate and severe hepatic impairment relative to subjects with normal liver function (Figure 13). These results are consistent with literature reports (Fischer 1996).

Higher systemic exposures of OCA were also observed in patients with hepatic impairment, especially those with moderate and severe hepatic impairment demonstrating that the PK profile of OCA is consistent with that expected of the endogenous bile acid CDCA.

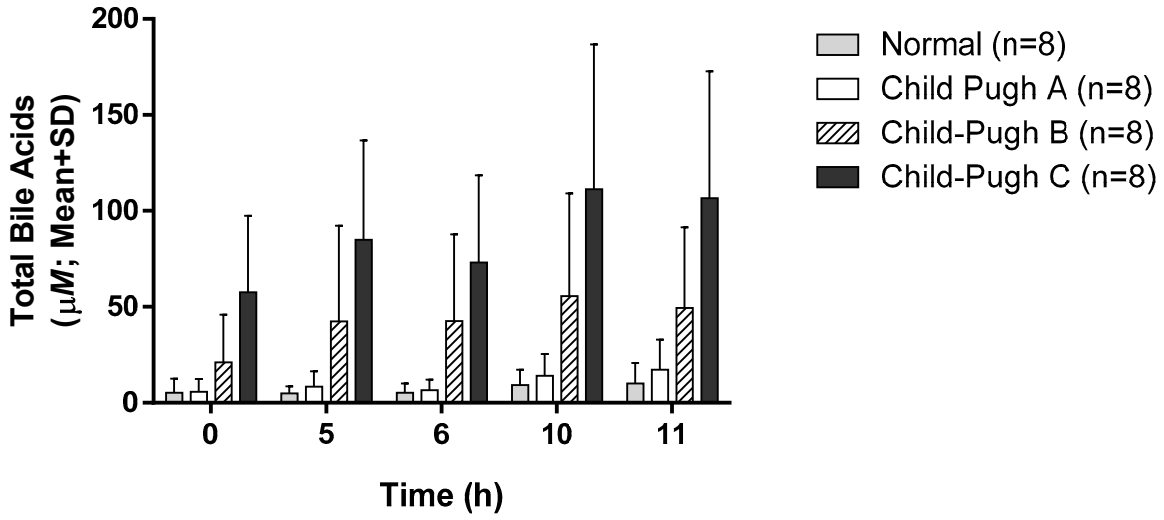
Liver exposure of bile acids are only modestly higher (approximately 2-fold) in patients with end stage liver disease (Fischer 1996), which is consistent with modeling and simulations of OCA. The liver is the primary site of action for the safety and efficacy of OCA along with the intestine. Therefore, the modest increase in liver exposure with hepatic impairment is not expected to significantly affect the safety and efficacy profile of OCA.

Modeling and simulation for OCA also suggests that high systemic exposure of OCA observed in patients with hepatic impairment is not likely to result in liver toxicity, since exposure in the liver was not predicted to be at levels expected to induce liver toxicity (elevated transaminases). This is consistent with observed safety data, which indicate that no specific safety concerns were evident in patients with moderate to severe hepatic impairment.

A modified dosing regimen of OCA is recommended in patients with moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) to establish tolerability, after which, increasing dose frequency may occur based on response.

No dosage adjustment is needed in patients with mild hepatic impairment (Child-Pugh Class A).

Figure 13: Endogenous Bile Acid Exposure in Healthy Subjects and in Patients with Hepatic Impairment (747-103)



4.4.3. Renal Impairment

Human absorption, distribution, metabolism, and elimination (ADME) studies with OCA have showed negligible urinary excretion and that renal clearance is likely to have minimal role in the elimination of OCA. Based on these results, no dose adjustment is necessary for patients with renal impairment.

4.5. Effect of Extrinsic Factors on Pharmacokinetics

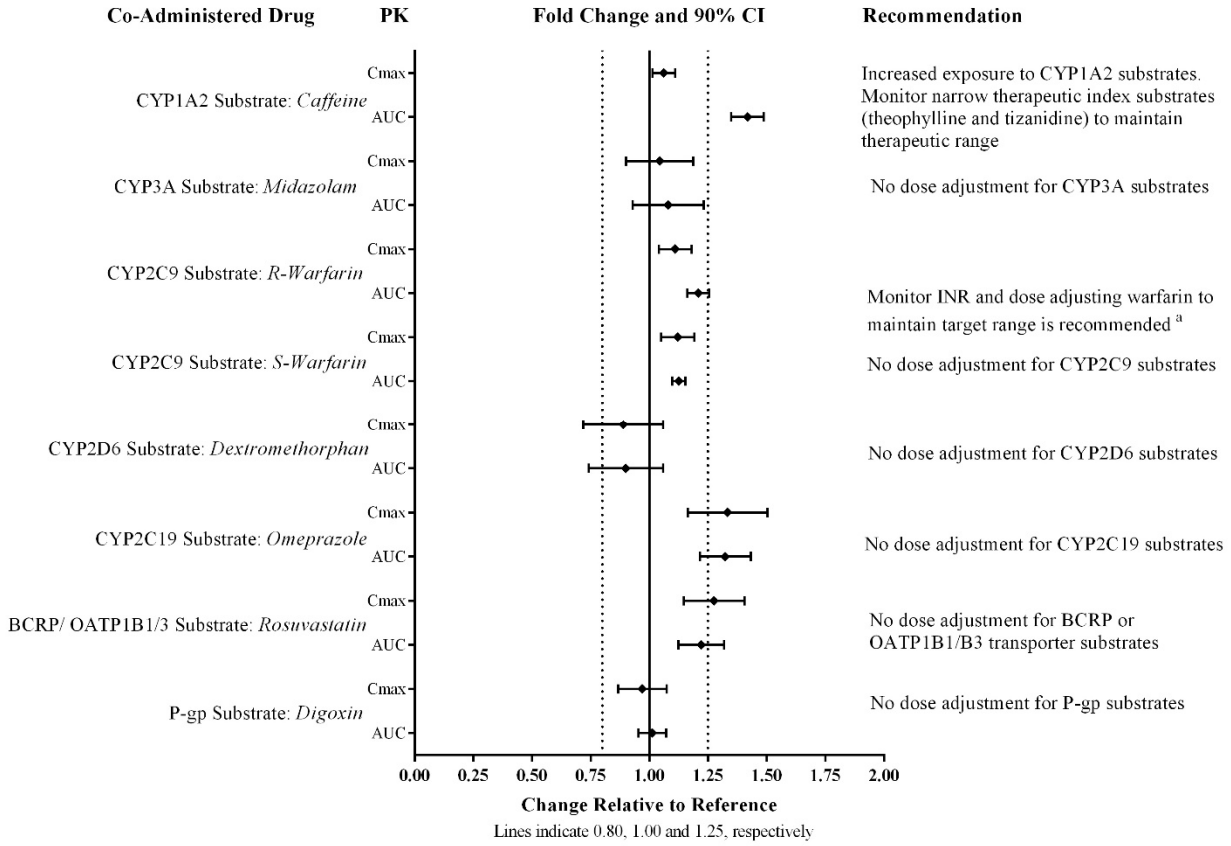
4.5.1. Drug Interaction Studies

OCA showed no or weak effects on the major drug metabolism enzymes and transporters.

4.5.1.1. Potential for OCA to Affect Other Drugs

OCA has been extensively studied with commonly used probes to characterize potential drug interactions across *in vitro* and clinical studies. Results from these studies show minimal to no effects for major cytochrome P450 enzymes and human transporters. Clinical drug-drug interaction studies were conducted during the development program of OCA and the results are presented in Figure 14.

Figure 14: Results from OCA Clinical Drug-Drug Interaction Studies using Probes for Cytochrome P450 Enzymes and Major Human Transporters



[a] There was no change in CYP2C9 mediated metabolism of warfarin; however, a modest decrease in INR was observed.

4.5.1.2. Potential for Other Drugs to Affect OCA

Bile acid binding resins may modestly reduce the exposure and efficacy of OCA.

Bile acid binding resins such as cholestyramine, colestipol, and colesevelam adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of OCA. Bile acid binding resins should be taken at least 4 hours before or 4 hours after OCA (or at as great an interval as possible) to minimize any effects.

4.5.2. Assessment of QTc Interval Prolongation

OCA does not cause QT prolongation at therapeutic and supra-therapeutic doses.

Study 747-108 examined the ability to detect cardiovascular effects on QT intervals in healthy subjects by OCA and its conjugates after administration of therapeutic and supra-therapeutic doses (up to 100 mg daily for 5 days). Markers for other cardiovascular safety events, including tachycardia, were not observed in patients receiving OCA. On Day 5 of dosing, the largest

difference in ΔΔQTcF was 3.2 mseconds with an adjusted upper 95% confidence limit (CL) of 6.5 mseconds. Guidance criteria for monitoring change from baseline (+10 mseconds threshold) showed no relationship between QT prolongation and exposure to OCA or its conjugates.

5. CLINICAL EFFICACY IN PBC

5.1. Phase 2 Study Designs and Statistical Plans

Studies 747-201 and 747-202 were 3-month Phase 2 studies that informed the Phase 3 study design.

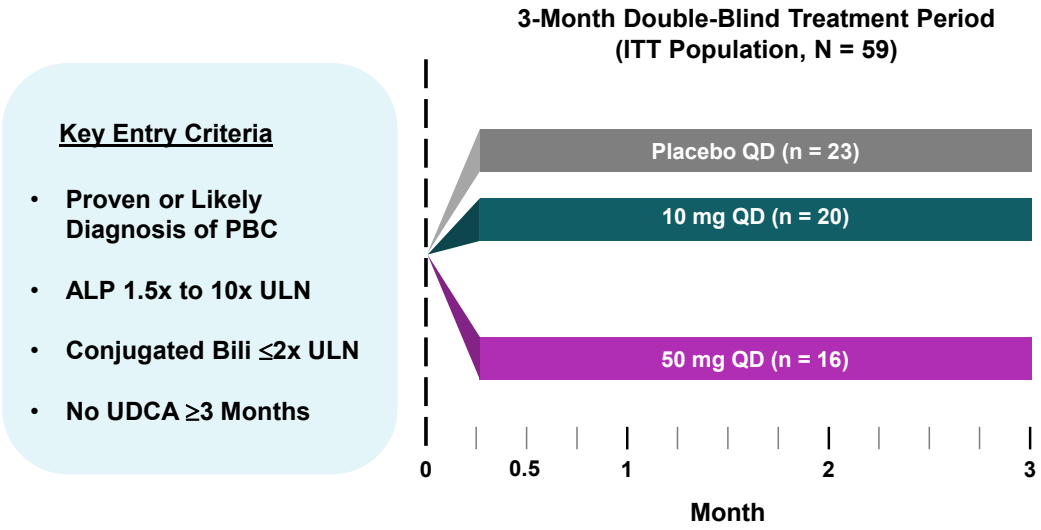
Studies 747-201 and 747-202 were international, multicenter, randomized, double-blind, placebo-controlled, multi-dose, parallel group studies in patients with a proven biopsy or probable diagnosis of PBC (Figure 15). These Phase 2 studies evaluated OCA as monotherapy (747-201) and in combination with UDCA (747-202).

To qualify, patients were to have not been administered UDCA for at least 3 months prior to screening in the monotherapy study (747-201) or had to have been taking a stable dose of UDCA in the UDCA combination study (747-202).

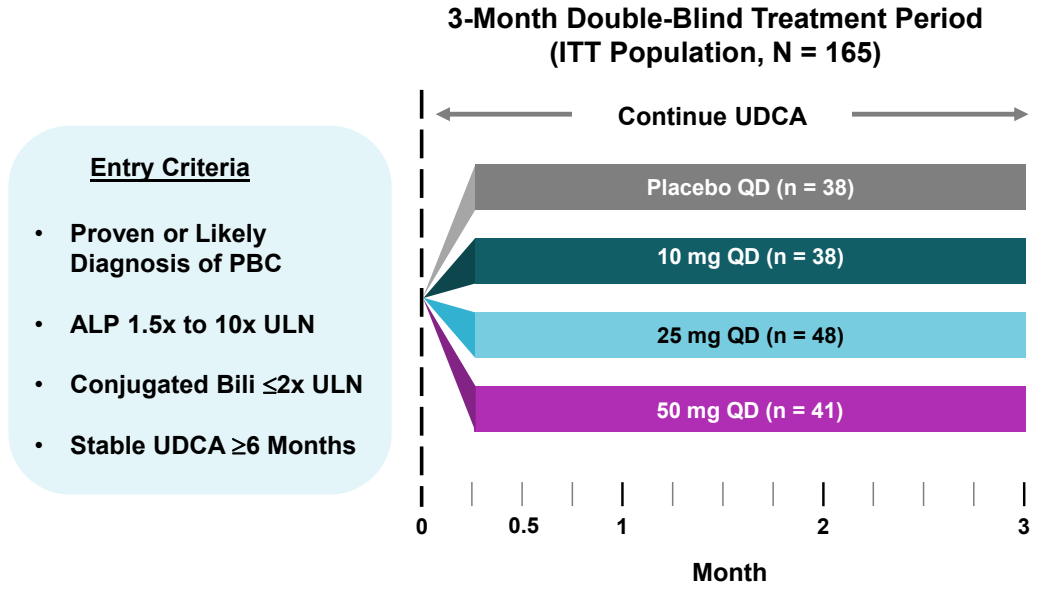
Once daily doses of placebo, OCA 10 mg, or OCA 50 mg for Study 747-201 and placebo, OCA 10 mg, OCA 25 mg, or OCA 50 mg (and UDCA) for Study 747-202 were used. After the double-blind phase, some patients enrolled into an open-label, long-term safety extension LTSE; one LTSE is ongoing.

Figure 15: Phase 2 Study Designs

Study 747-201 (Monotherapy)



Study 747-202 (Combination with UDCA)



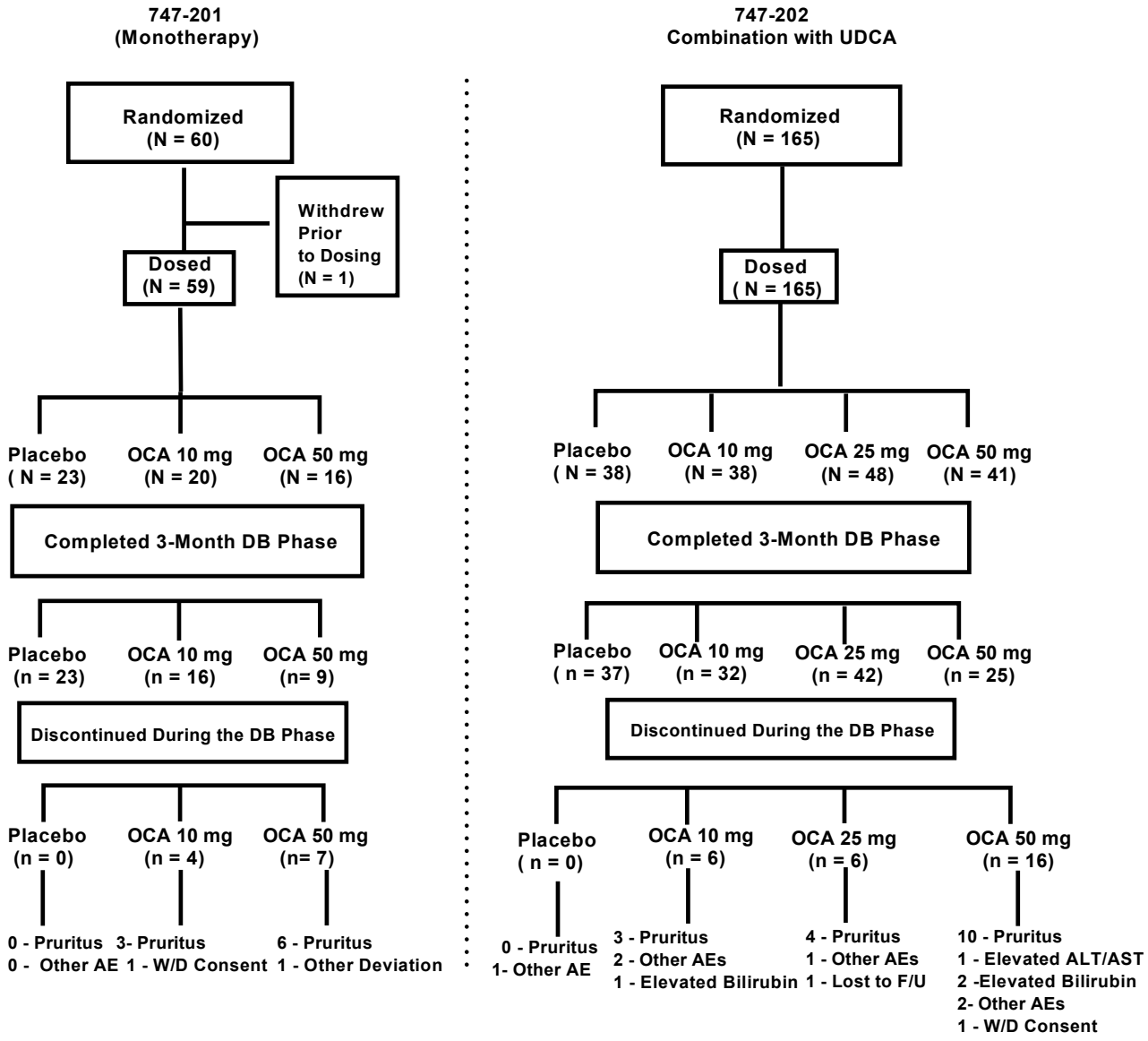
ITT= intent-to-treat; PBC= primary biliary cirrhosis; QD = once daily; UDCA = ursodeoxycholic acid;
ULN = upper limit of normal
ITT population included all randomized patients who received at least 1 dose of investigational product based on the treatment group assignment.

As expected, Baseline ALP values were higher for patients who were not on UDCA (747-201).

The primary measure of efficacy in Studies 747-201 and 747-202 was the percent change in ALP from baseline to end of study (3 months).

The majority (>80%) of patients within each Phase 2 study completed the double-blind phase (Figure 15). Pruritus was the main reason for discontinuation in each Phase 2 study. A total of 26 OCA-treated patients discontinued due to pruritus (9 in Study 747-201 and 17 in Study 747-202). A total of 16 (62%) of the 26 discontinuations due to pruritus occurred at OCA doses >10 mg (ie, 25 mg or 50 mg). No placebo-treated patients in the 3 studies discontinued due to pruritus. Three patients (1 OCA 10 mg, 2 OCA 50 mg) discontinued due to a 2-fold increase in conjugated bilirubin and 1 patient discontinued (1 OCA 50 mg) due to a 3-fold increase in ALT.

Figure 16: Patient Disposition; Double-Blind, Placebo-Controlled, Phase 2 Studies



Note: Studies 747-201 and 747-201 had mandatory protocol discontinuation criteria if ALT or AST ≥3x average predose value (average of Screening and Baseline) and >ULN or conjugated bilirubin >2x average predose value, and >ULN (25.7 µmol/L or 1.5 mg/dL).

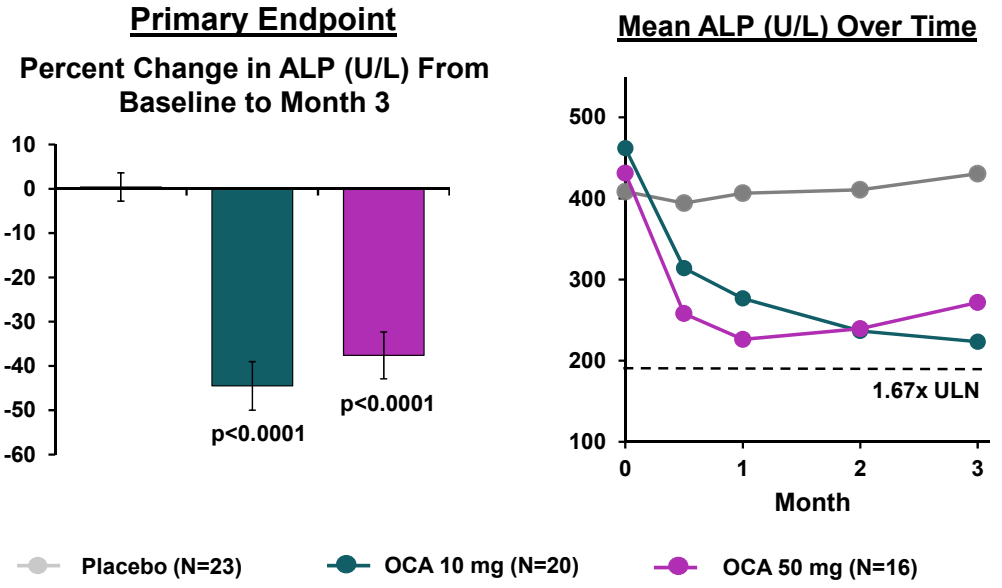
5.1.1. Phase 2 Efficacy Results

The primary endpoint was achieved in both Phase 2 studies, with a significant reduction in ALP at 3 months with OCA treatment compared with placebo. Statistically significant improvements were also observed in secondary biochemical analytes reflective of hepatic damage and function in both studies. No incremental benefit in efficacy was observed at doses greater than 10 mg when OCA was administered either alone or in combination with UDCA.

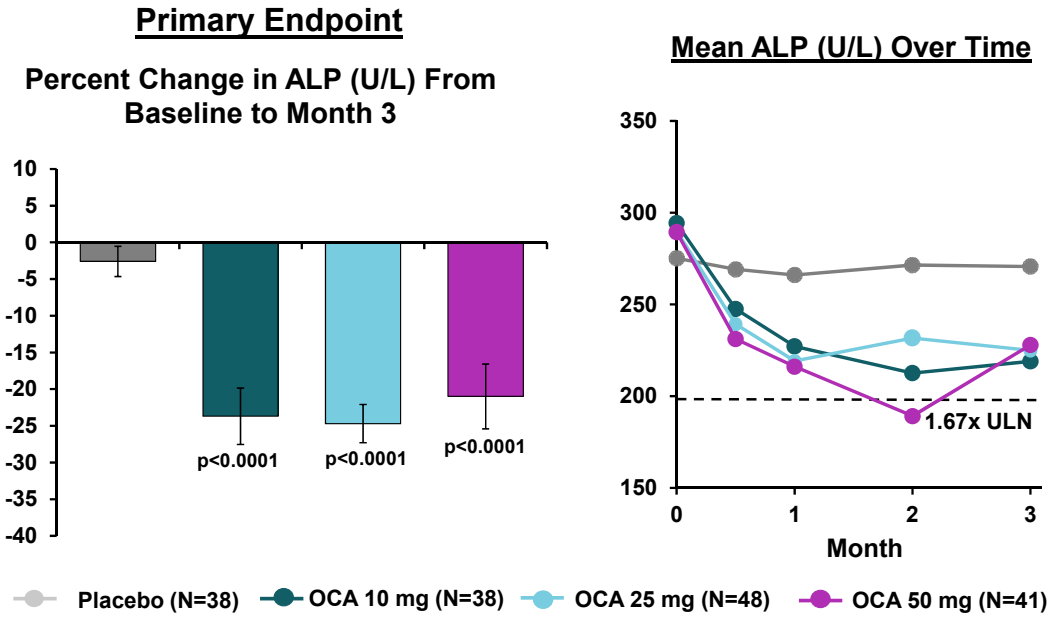
Treatment with OCA for 3 months in patients with PBC resulted in statistically and clinically significant reductions in ALP (Figure 17), a known surrogate for risk of long-term clinical outcomes in PBC, as well as markers of hepatic damage and inflammation. Consistent efficacy results were observed irrespective of whether OCA was provided as monotherapy or as add-on to UDCA. Within each study, OCA doses above 10 mg did not show substantially better efficacy compared with OCA 10 mg, but the incidence and severity of pruritus was increased (see Section 6.7.1), suggesting that 10 mg was the maximally efficacious dose and that evaluation of lower doses in the Phase 3 program was warranted.

Figure 17: Primary Endpoint Achieved in Phase 2 Studies (ITT)

Study 747-201 (Monotherapy)



Study 747-202 (Combination with UDCA)



The primary efficacy endpoint was analyzed using the 2-sided Wilcoxon-Mann-Whitney test.

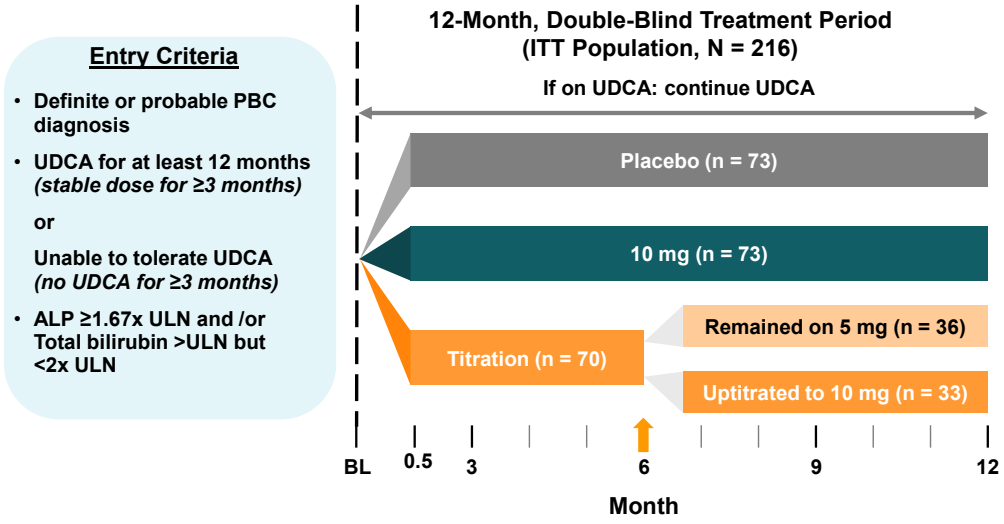
5.2. Phase 3 Study Design and Statistical Plan

The Phase 3 study was designed to evaluate OCA in patients with PBC in combination with UDCA, which is the current standard of care. A small minority of patients unable to tolerate UDCA were also included in the study.

Study 747-301 was an international, randomized, double-blind, placebo-controlled, parallel-group, 12-month study evaluating OCA in patients with PBC who were either taking UDCA or unable to tolerate UDCA (Figure 18). Patients were randomized to receive placebo, OCA 5 mg, or OCA 10 mg for the first 6 months. At Month 6, patients in the OCA 5 mg (titration) group who did not achieve the primary endpoint and tolerated drug titrated from OCA 5 mg to 10 mg for the final 6 months.

Patients continued their pre-study UDCA dose or, in those patients who were unable to tolerate UDCA, received OCA (or placebo) as monotherapy.

Figure 18: Study Design (Phase 3)



ITT= intent-to-treat; PBC= primary biliary cirrhosis; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

The ITT population (all randomized patients who received at least 1 dose of investigational product) was used for baseline and efficacy and safety data analyses.

Table 3: Efficacy Endpoints (Phase 3)

Primary Endpoint: Percentage of patients (OCA 10 mg vs placebo) achieving composite endpoint at Month 12 (the percentage of patients reaching an ALP <1.67x ULN and a ≥15% reduction in ALP and a total bilirubin ≤ULN)
Key Secondary Endpoint: Percentage of patients (OCA titration vs placebo) achieving composite endpoint at Month 12
Other Secondary Endpoints:
Absolute and percent change from Baseline in ALP, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), AST, total bilirubin, conjugated (direct) bilirubin, albumin, prothrombin time and international normalized ratio (INR) at all timepoints
Percentage of patients with a decrease in ALP of ≥10%, ≥15%, ≥20%, and ≥40% from Baseline or ≤ULN
Absolute change from Baseline at Month 12 for enhanced liver fibrosis (ELF) and hepatic stiffness (at select sites) as assessments of end stage liver failure
Absolute and percent change from Baseline at all timepoints on c-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), fibroblast growth factor-19 (FGF-19) levels, interleukin-6 (IL-6), and cytokeratin-18 (CK-18)
Absolute and percent change from Baseline at all timepoints on PBC domains.
Exploratory Endpoints:
Exploratory endpoints included absolute and percent change from Baseline on PBC autoantibodies (immunoglobulin A [IgA], immunoglobulin G [IgG], immunoglobulin M [IgM]) and interleukins (IL-12 [p40], IL-23)

Statistical Analyses

Analyses for the primary composite endpoint compared placebo to the active OCA treatment groups using a Cochran–Mantel–Haenszel (CMH) test stratified by the randomization stratification factor based on the ITT population. Missing values were considered a non-response. The primary efficacy analysis of the composite endpoint compared the 10 mg OCA group to placebo. A hierarchical approach was used to control the overall significance level for key secondary efficacy analyses.

The key secondary efficacy endpoints were to be considered confirmatory only if the analysis of primary endpoint was statistically significant. A 2-sided test at the 5% level of significance was used for all endpoints.

The following rank order for the testing of statistical significance was used for the key secondary efficacy analyses:

- Pairwise comparison of OCA titration to placebo for the proportion of patients at Month 12 with ALP <1.67x ULN (with a decrease of ≥15% from baseline) and total bilirubin ≤ULN

If statistical significance was not achieved for an endpoint in the above ranking, the results of all subsequent analyses were not considered confirmatory.

Sensitivity analyses were performed on the primary efficacy endpoint using observed data only.

The CMH test was also used for ALP responder analyses, disease prognostic risk responder analyses, and subgroup responder analyses. Sensitivity analyses were performed using the ITT

population on all responder endpoints using a logistic regression model with response as the endpoint and treatment group and randomization strata as factors. Missing values were considered a non-response. Estimates of the odds ratio comparing OCA 10 mg to placebo and the 95% CI of the odds ratio were presented. An odds ratio greater than 1 favored the OCA treatment group.

Efficacy laboratory parameters (ALP, GGT, ALT, AST, total bilirubin, conjugated [direct] bilirubin, albumin, prothrombin time, and international normalized ratio) were analyzed using an analysis of covariance (ANCOVA) model with absolute change or percent change from baseline as the dependent variable including treatment group and randomization stratification factor as fixed effects and baseline as a covariate. Analyses of the clinical laboratory values were also carried out using the ITT population and a restricted maximum likelihood based on mixed-effect repeated measures model (MMRM) to evaluate the effect over time. In addition, the ANCOVA analyses of the clinical laboratory values on the ITT population were repeated using last observation carried forward (LOCF).

Other continuous/quantitative efficacy variables used the same methods as described for the efficacy laboratory parameters. These included enhanced liver fibrosis (ELF) and hepatic stiffness (at select sites) as assessments of end stage liver failure; c-reactive protein (CRP), TNF-α, transforming growth factor-beta (TGF-β), FGF-19 levels, interleukin-6 (IL-6), and Cytokeratin-18 (CK-18); and PBC-40 domains. Exploratory endpoints included PBC autoantibodies (immunoglobulin A [IgA], immunoglobulin G [IgG], immunoglobulin G [IgM]) and interleukins (IL-12 [p40], IL-23).

All safety analyses were based on the Safety population.

Patient Population (Phase 3)

Patients 18 years older with a definite or probable diagnosis of PBC (consistent with AASLD and EASL Practice Guidelines [Lindor 2009, EASL 2009]) were eligible for Study 747-301 and key inclusion and exclusion criteria are summarized in Table 4.

Table 4: Key Inclusion and Exclusion Criteria (Phase 3)

Diagnosis and Main Criteria for Inclusion:

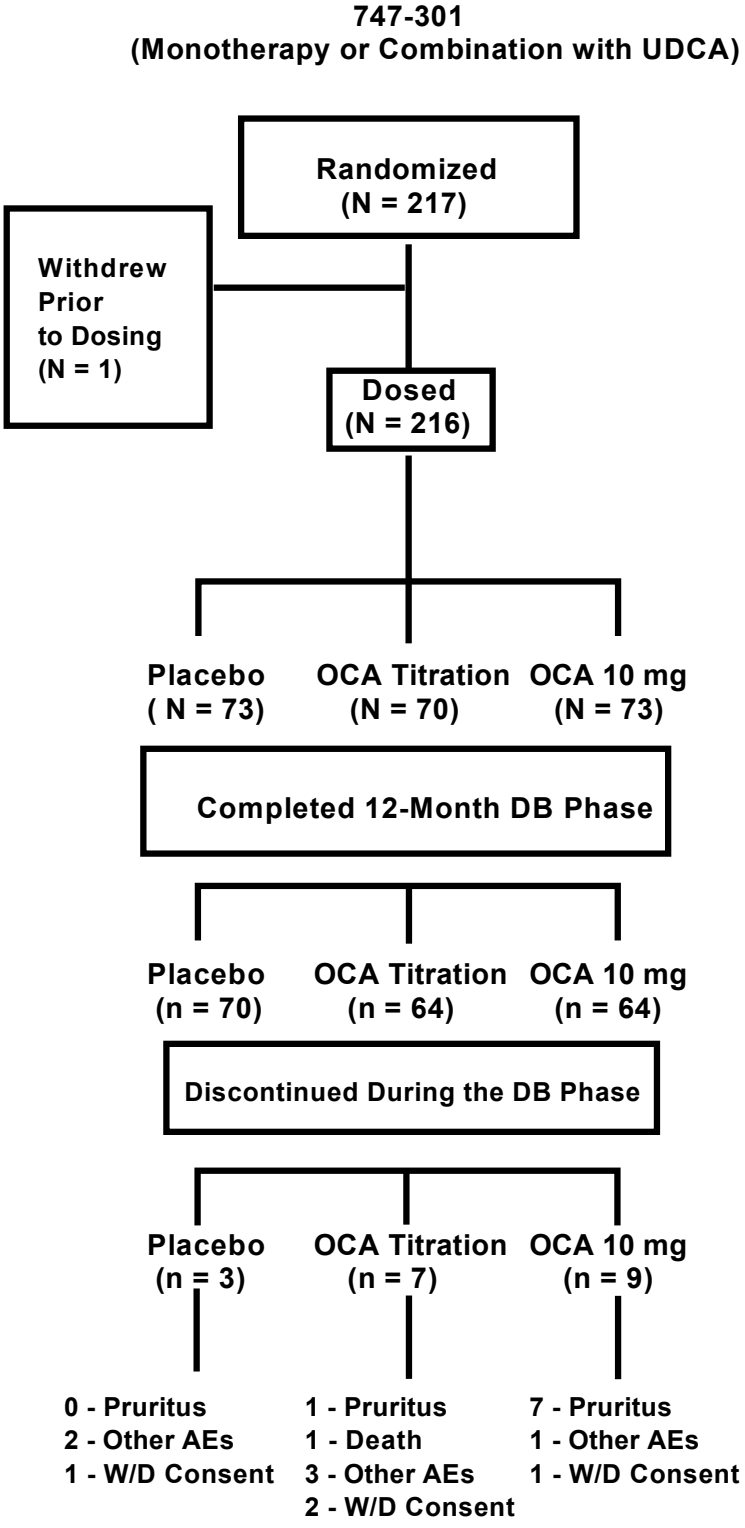
• Age ≥18 years with a definite or probable diagnosis of PBC
• At least 1 of the following qualifying biochemistry values:
  • ALP level ≥1.67x ULN
  • Total bilirubin >ULN but <2x ULN
Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 0, or unable to tolerate UDCA (no UDCA for ≥3 months) prior to Day 0

Main Criteria for Exclusion:
• Other concomitant liver diseases • Clinical complications of PBC or clinically significant hepatic decompensation (eg, variceal bleeds, encephalopathy, or poorly controlled ascites) • Severe pruritus or systemic treatment for pruritus (BAS or rifampicin) within prior 2 months

BAS = bile acid sequestrants; PBC= primary biliary cirrhosis; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

Patient disposition is summarized in A total of 70 (96%), 64 (90%), and 64 (88%) patients from the placebo, OCA titration, and OCA 10 mg treatment groups, respectively, completed the 12-month double-blind phase. Nineteen patients discontinued the double-blind phase prematurely: 1 (<1%) due to death (cardiac failure, OCA titration, unrelated); 8 (4%) due to pruritus; 6 (3%) due to other adverse events (AEs); and 4 (2%) due to withdrawn consent.

Figure 19: Patient Disposition; Double-Blind, Placebo-Controlled, Phase 3



Demographics and baseline characteristics were typical of a PBC population and included a high risk population of advanced or cirrhotic patients.

Demographics and baseline characteristics were typical of a PBC population, middle to advanced aged females, and reflective of a high-risk population primarily earlier in disease but with fair (~30%) representation of more advanced or cirrhotic patients (based on current or prior evidence of cirrhosis), 9% of patients had elevated bilirubin levels at baseline). Demographics and baseline-disease characteristics were well balanced between treatment arms (Table 5).

Table 5: Demographic and Baseline Characteristics; Double-Blind, Placebo-Controlled, Phase 3 (ITT Population)

Number of Patients	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)	Total (N = 216)
Age (years)				
Mean (SD)	55.5 (10.0)	55.8 (10.5)	56.2 (11.0)	55.8 (10.5)
Median	55.0	54.5	56.0	55.0
Min, Max	35, 78	29, 83	30, 86	29, 86
Age Subgroups, n (%)				
<65 years	60 (82)	60 (86)	56 (77)	176 (81)
≥65 years	13 (18)	10 (14)	17 (23)	40 (19)
Sex, n (%)				
Male	5 (7)	5 (7)	10 (14)	20 (9)
Female	68 (93)	65 (93)	63 (86)	196 (91)
Race/Ethnicity, n (%)				
White	66 (90)	67 (96)	70 (96)	203 (94)
Non-White	7 (10)	3 (4)	3 (4)	13 (6)
Disease Stage				
Cirrhotic[a], n (%)	9 (12)	7 (10)	4 (5)	20 (9)
Advanced Disease Stage[b], n (%)	30 (41)	22 (31)	20 (27)	72 (33)
UDCA Dose at Baseline, mg/kg				
Dose	15 ± 4	17 ± 5	16 ± 5	16 ± 5
Age at PBC Diagnosis Baseline				
Years	47 ± 9	48 ± 12	47 ± 11	47 ± 11
≤50 years, n (%)	45 (62)	38 (54)	42 (58)	91 (58)
ALP (U/L)				
Mean (SD)	327.5 (115.0)	325.9 (116.2)	316.3 (103.9)	323.2 (111.4)
Min, Max	143.8, 745.9	186.8, 811.0	207.1, 619.5	143.8, 811.0
≤3x ULN, n (%)	50 (68)	51 (73)	53 (73)	154 (71)
>3x ULN, n (%)	23 (32)	19 (27)	20 (27)	62 (29)
Total Bilirubin (µmol/L)				
Mean (SD)	11.8 (7.4)	10.3 (5.5)	11.3 (6.7)	11.5 (6.6)
Min, Max	2.3, 39.3	2.1, 36.4	1.6, 34.4	1.6, 39.3
≤ ULN, n (%)	66 (90)	66 (94)	66 (90)	198 (92)
> ULN to <2x ULN, n (%)	7 (10)	4 (6)	7 (10)	18 (8)

ALP = alkaline phosphatase; ITT= intent-to-treat; PBC= primary biliary cirrhosis; SD = standard deviation; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

[a] Cirrhosis based on an initial or baseline "in study" biopsy result or patients with an Ishak score 6 (cirrhosis) or Ludwig/Scheuer PBC Stage 4.

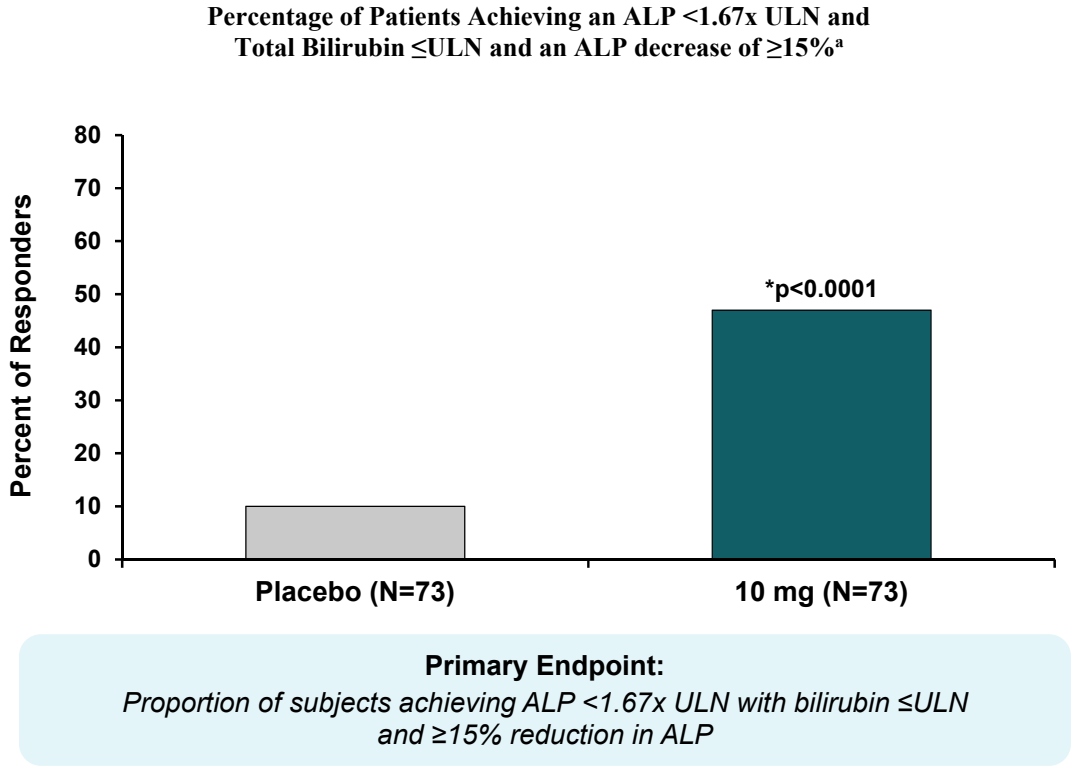
[b] Advanced disease progression was a post hoc analyses defined as a patient meeting at least one of the following criteria: Baseline total bilirubin >ULN; Baseline total ALP >5X ULN; Baseline transient elastography >10.7 kPA; Cirrhosis based on an initial or baseline "in study" biopsy result or patients with an Ishak score 6 (cirrhosis) or Ludwig/Scheuer PBC Stage 4; or a medical history of interest of (ie, ascites, hepatic cirrhosis, jaundice, portal hypertension, portal hypertensive gastropathy, or varices esophageal).

5.2.1. Phase 3 Efficacy Results

The Phase 3 study met its primary endpoint. Both OCA treatment groups (OCA titration and OCA 10 mg) were superior to placebo in achieving the primary endpoint at all timepoints across the 12-month treatment period (p <0.0001 versus placebo).

At Month 12, a total of 34 (47%) patients from the OCA 10 mg group achieved the composite endpoint, compared with 7 (10%) patients from the placebo group (p <0.0001) (Figure 20).

Figure 20: Percentage of Patients Achieving Primary Efficacy Composite Endpoint at Month 12 Using Imputed Data; Double-Blind, Placebo-Controlled, Phase 3 (ITT Population)



ALP = alkaline phosphatase; ITT= intent-to-treat; ULN = upper limit of normal
[a] Missing values were considered a non-response.
* p-value obtained using CMH test stratified by randomization strata factor.

Comparable efficacy was observed between the OCA titration arm and the 10 mg fixed dose at 12 months (Table 6).

Table 6: Percentage of Patients Achieving the Primary Composite Endpoint at Month 6 and Month 12; Double-Blind, Placebo-Controlled, Phase 3 (ITT Population)

	Percentage of Patients Achieving an ALP <1.67x ULN and Total Bilirubin ≤ULN and an ALP decrease of ≥15%[a]		
		OCA	
	Placebo (N = 73)	Titration[b] (N = 70)	10 mg (N = 73)
Month 6			
Dose	-	5 mg	10 mg
Responders, n (%)	5 (7)	24 (34)	37 (51)
p-value 5 mg vs 10 mg	NA	NA	**0.0358**
p-value vs placebo[c]	NA	**<0.0001**	**<0.0001**
Month 12			
Dose	-	5 mg or 10 mg	10 mg
Responders, n (%)	7 (10)	32 (46)	34 (47)
p-value vs placebo[c]	NA	**<0.0001**	**<0.0001**

ALP = alkaline phosphatase; ITT= intent-to-treat; SD = standard deviation; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

[a] Missing values were considered a non-response.

[b] Patients randomized to OCA titration received OCA 5 mg for the initial 6-month period. At Month 6, patients who did not achieve the composite endpoint and did not have evidence of tolerability issues were titrated from 5 mg to 10 mg for the final 6 months of the double-blind phase.

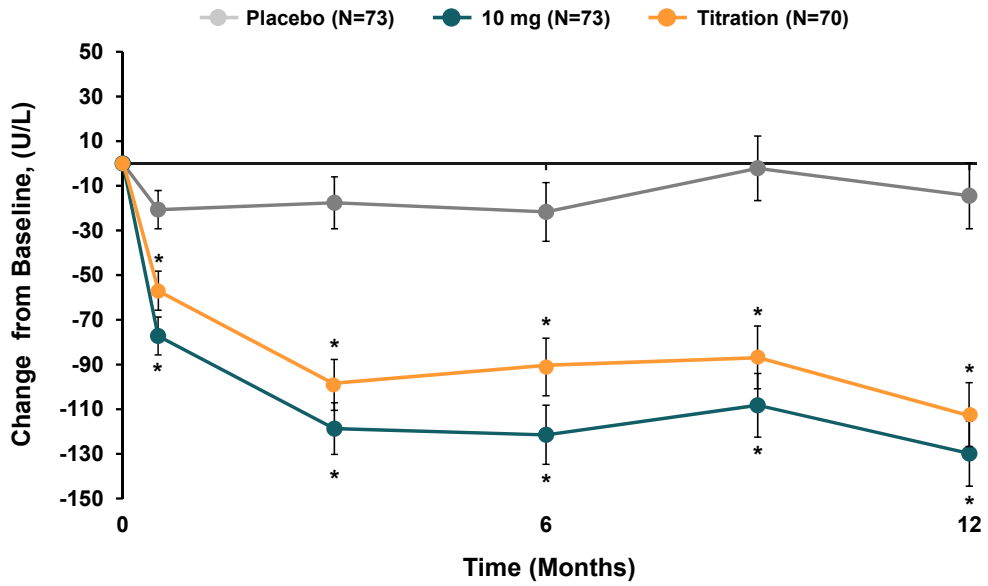
[c] p-values for comparing OCA versus placebo are obtained using CMH by randomization strata factor.

ALP and Total Bilirubin

The response to OCA therapy was rapid and robust with significant reductions in ALP apparent within 2 weeks of treatment and at every time point thereafter. Mean total bilirubin levels increased in the placebo group and were maintained for the OCA treatment groups, suggestive of a slowing of disease progression with OCA.

The reductions in ALP were achieved in both OCA groups, reductions being numerically greater with the higher 10 mg dose of OCA over the course of the study (Figure 21). With OCA treatment reductions in ALP were 33% and 39%, respectively, for the OCA titration and OCA 10 mg groups, which resulted in Month 12 values approaching 1.67x ULN for OCA-treated patients compared to placebo with ALP levels nearing 3x ULN.

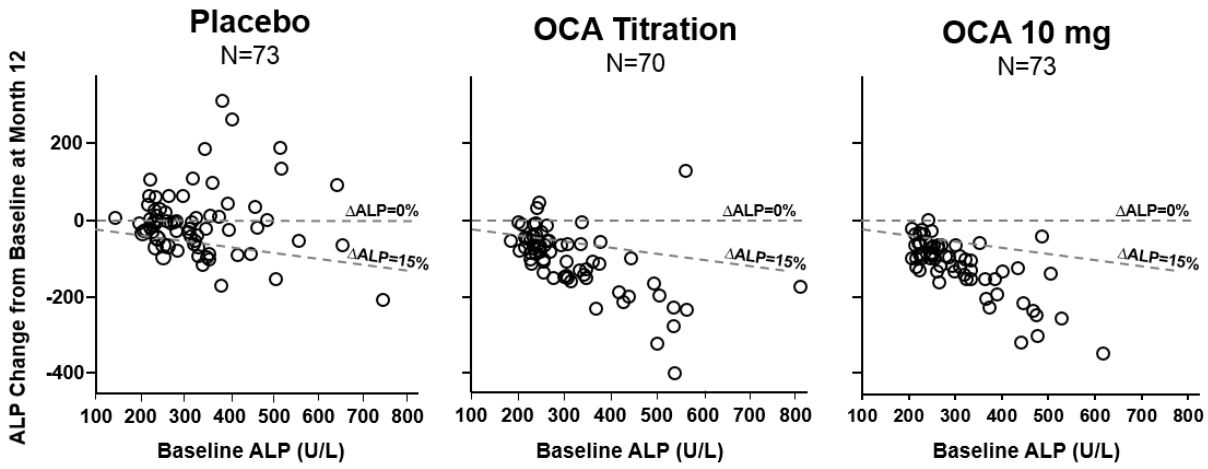
Figure 21: Significant Reductions in ALP (U/L) Observed Early and Sustained; Double-Blind, Placebo-Controlled, Phase 3 (ITT Population)



ALP = alkaline phosphatase; ITT= intent-to-treat; LS= least square; OCA = obeticholic acid; PBC= primary biliary cirrhosis; SD = standard deviation; SE = standard error; ULN = upper limit of normal
Change from baseline is LS mean

Change in ALP from Baseline to Month 12 by patient is presented in Figure 22. The majority (77%) of patients from both OCA groups achieved a reduction of at least 15% in ALP at 12 months compared to 29% of patients on placebo. In addition, 36% of patients treated with placebo experienced an increase in ALP compared to 5% and 2% of patients from the OCA titration and OCA 10 mg groups, respectively. OCA's impact on ALP improvement in the majority of patients is particularly notable given the log-linear relationship of ALP and transplant free survival (ie, the lower the ALP, the greater the risk reduction).

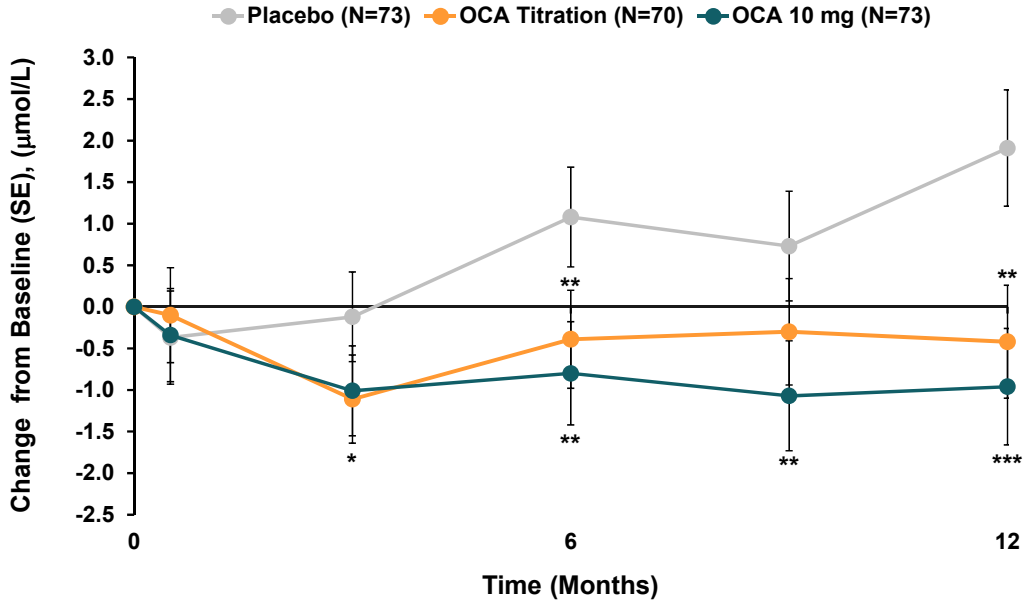
Figure 22: Observed Individual Patient Change in ALP from Baseline at Month 12; Double-Blind, Placebo-Controlled, Phase 3 (ITT Population)



ALP = alkaline phosphatase

Bilirubin levels, while normal at baseline, appeared to deteriorate in the placebo group despite continued use of UDCA. This was in contrast to OCA-treated patients whose bilirubin stabilized and in some cases tended to improve (Figure 23).

Figure 23: Change in Total Bilirubin (µmol/L) Over Time; Double-Blind, Placebo-Controlled, Phase 3 (ITT Population)



OCA = obeticholic acid; SE = standard error
* $p < 0.0001$; ** $p < 0.01$; * $p < 0.05$
Change from baseline is LS mean

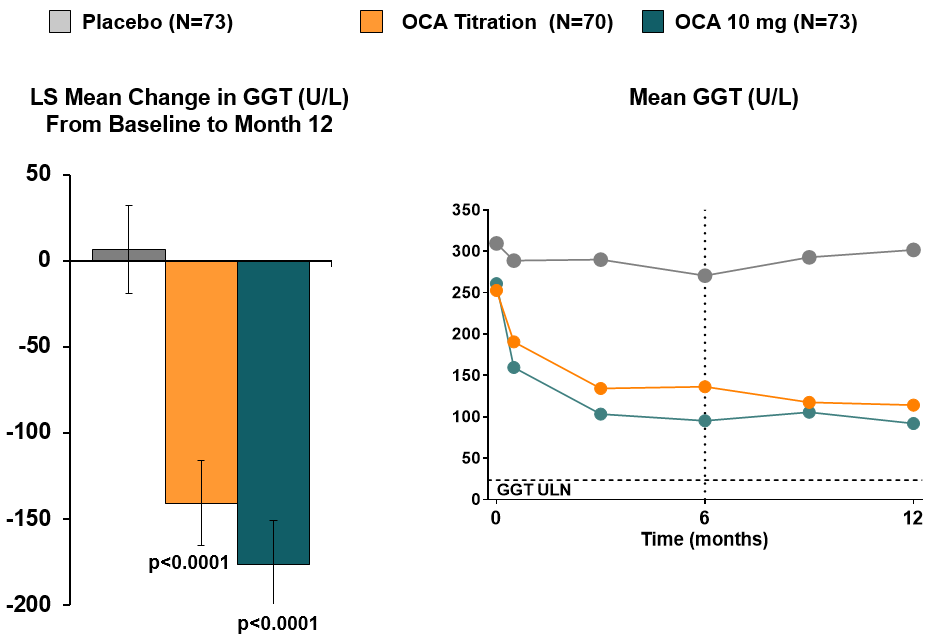
Other Liver Biochemistry Parameters

Patients treated with OCA titration and OCA 10 mg had clinically meaningful and statistically significant decreases from baseline in GGT, ALT, and AST, further establishing the anti-cholestatic effects and suggesting a potential amelioration of hepatic cell injury with OCA in PBC.

GGT, ALT, and AST values over time are summarized in Figure 24 and Figure 25. Baseline GGT values were substantially elevated across all 3 treatment groups (approximately 10x ULN to 13x ULN), reflecting the significant cholestatic pattern of PBC. Mean hepatocellular transaminases (ALT and AST), which reflect hepatocellular injury, were also elevated, but to a lower extent.

Patients treated with OCA titration and OCA 10 mg had clinically meaningful and statistically significant decreases from baseline in all 3 laboratory parameters (GGT, ALT, and AST). Improvements were seen early and were sustained.

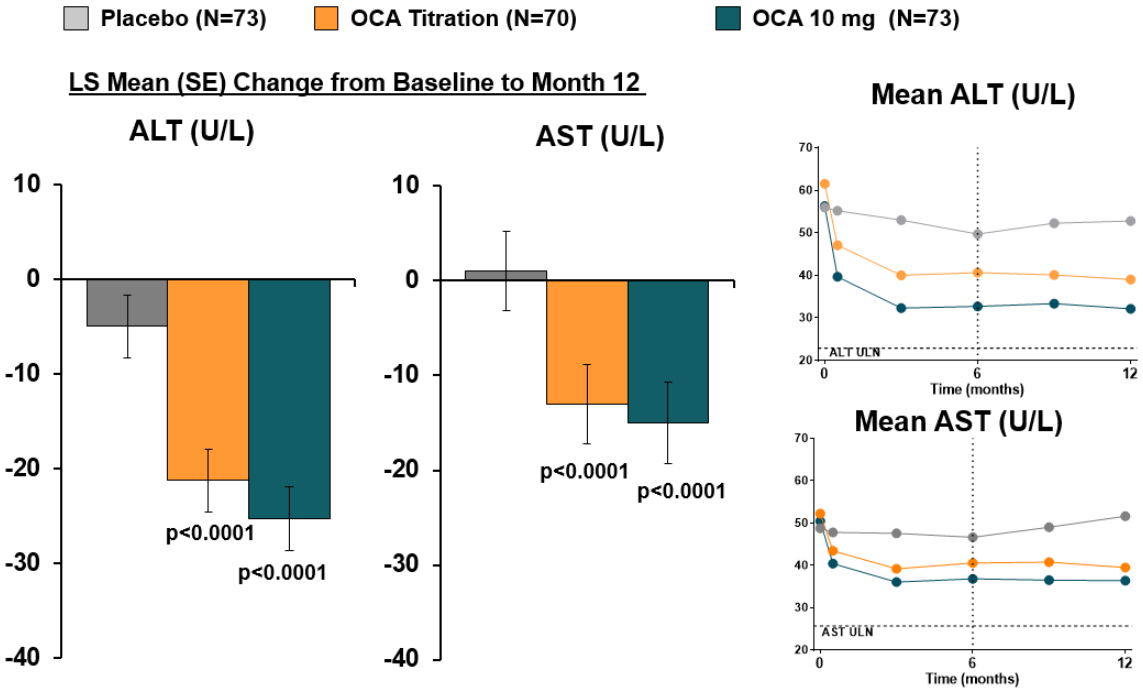
Figure 24: OCA Treatment Improves GGT; Double-Blind, Placebo-Controlled, Phase 3 (ITT Population)



P-value for comparing active treatments to placebo is obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment, double-blind Baseline UDCA usage (yes/no) and double-blind Baseline total bilirubin (≤ULN/>ULN).

GGT = gamma-glutamyl transferase; ITT= intent-to-treat; LS= least square; OCA = obeticholic acid; ULN = upper limit of normal

Figure 25: OCA Treatment Improves ALT and AST; Double-Blind, Placebo-Controlled Phase 3 (ITT Population)



P-value for comparing active treatments to placebo is obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment, double-blind Baseline UDCA usage (yes/no) and double-blind Baseline total bilirubin (≤ULN/>ULN).

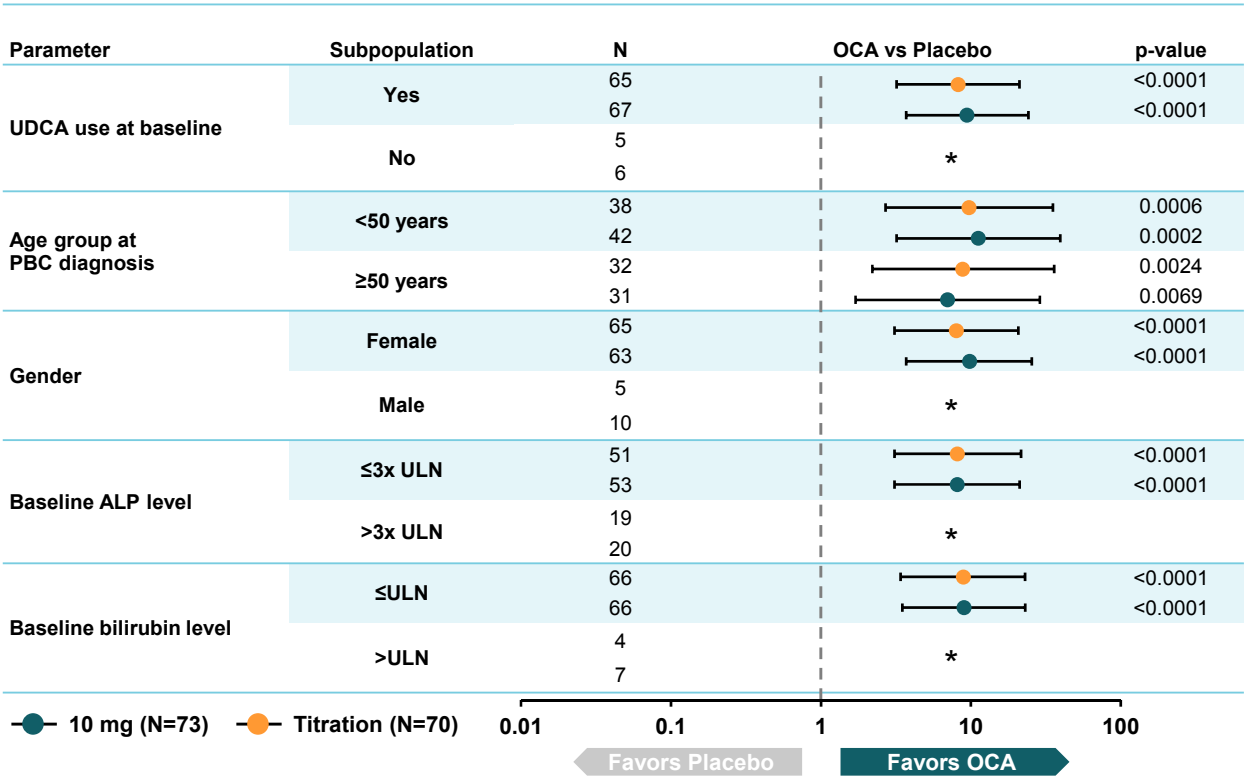
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ITT= intent-to-treat; LS= least square; OCA = obeticholic acid

Subgroup Analyses

The response across a range of subpopulations of interest, primarily those known to be risk factors for poor prognosis, provides a strong assessment on internal validity for the observed effect. These data also suggest that those patients with PBC with the highest risk are able to respond to OCA.

Pre-specified key subgroup analyses for OCA included: UDCA use at baseline, age group at diagnosis, gender, baseline ALP level, and baseline bilirubin level. Sensitivity analyses were performed using a logistic regression model with response as the endpoint and treatment group and randomization strata as factors to estimate the odds of being a responder with each OCA group relative to placebo (an odds ratio greater than 1 favored the OCA treatment group) (Figure 26). For the primary composite endpoint, improvements in OCA were consistently in favor of the OCA arm (95% CI >1). Odds ratio could not be calculated for monotherapy (no UDCA), males, baseline ALP >3x ULN, or baseline total bilirubin >ULN subgroups because no placebo patients in these groups who achieved the primary composite endpoint, which is notable by itself. Younger age at PBC diagnosis and male patients have been associated with a worse prognosis (Carbone 2013).

Figure 26: Odds Ratio (95% CI) of Composite Endpoint by High Risk Subpopulations; Double-Blind, Placebo-Controlled Phase 3 (Month 12)



ALP = alkaline phosphatase; OCA = obeticholic acid; ULN = upper limit of normal
*No placebo-treated patients achieved the primary composite endpoint.

5.2.2. Subgroups Within the OCA Titration Group

OCA titration from 5 mg to 10 mg resulted in a greater proportion of patients achieving the composite endpoint and an incremental improvement in ALP at Month 12 compared to those patients who remained on OCA 5 mg.

A total of 69 patients from the OCA titration group completed Month 6. Of these, 36 (52%) remained at 5 mg for the duration of the 12-month treatment period and 33 (48%) who did not meet the primary composite endpoint but tolerated the investigational product titrated to 10 mg for the last 6 months of the 12-month period. Thirteen (39%) of the patients who uptitrated met the composite endpoint at Month 12, demonstrating that significant incremental benefit can be gained with titration of OCA (Figure 27). Additional improvement in ALP was observed for the subset of patients within the OCA group who uptitrated to OCA 10 mg at Month 6. For this subset of patients, mean ALP was 348.1 U/L, 255.9 U/L, and 222.4 U/L for Baseline, Month 6, and Month 12, respectively (Figure 28).

Figure 27: Effect of Titration from OCA 5 mg to OCA 10 mg; Double-Blind, Placebo-Controlled, Phase 3 (Non-Responders in OCA Titration Group at Month 6)

Non-Responders at Month 6 (OCA Titration, n = 33)

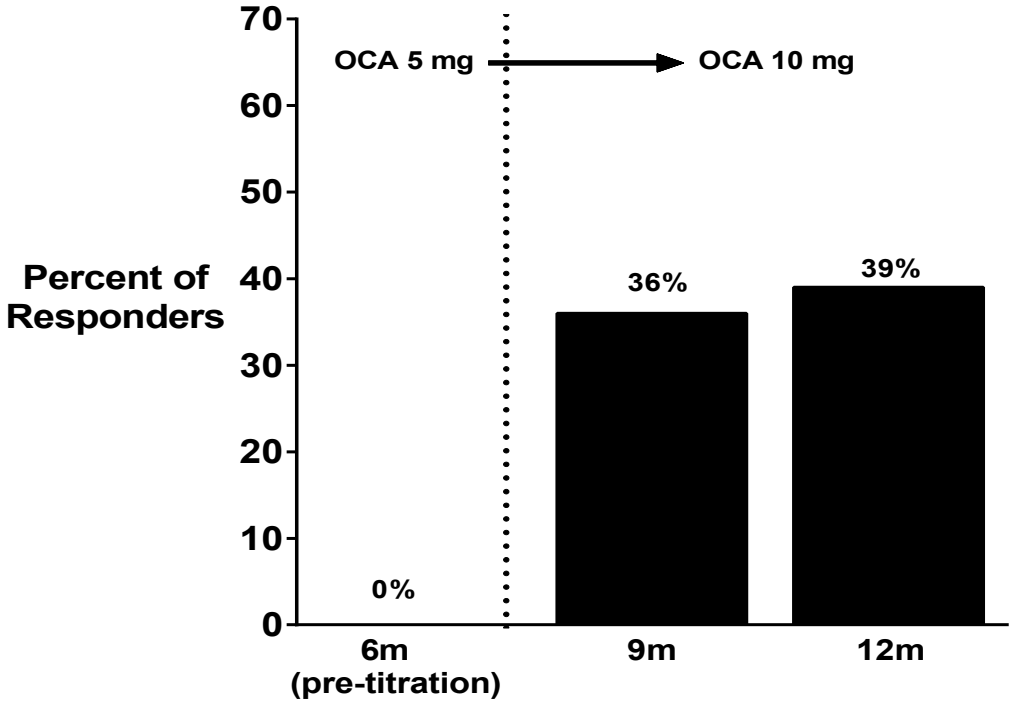
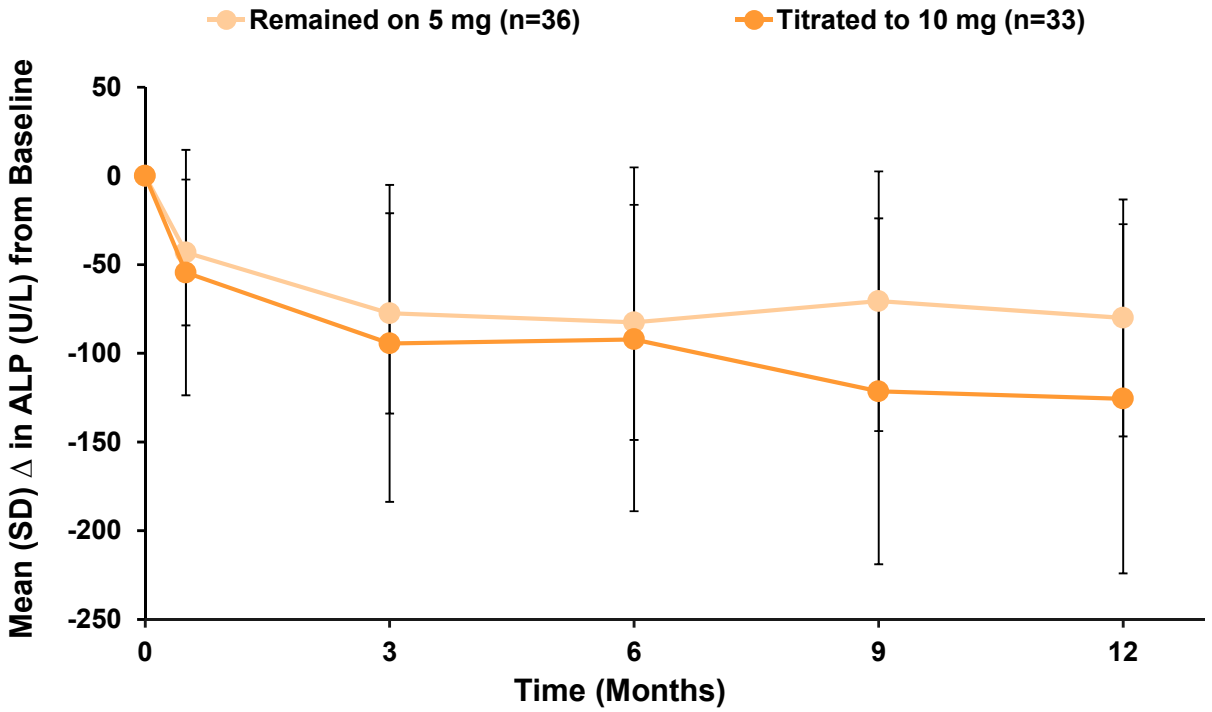


Figure 28: Mean (SD) ALP Over Time; Double-Blind, Placebo-Controlled Phase 3 (Titration Subgroup)



5.2.3. Advanced Disease Population

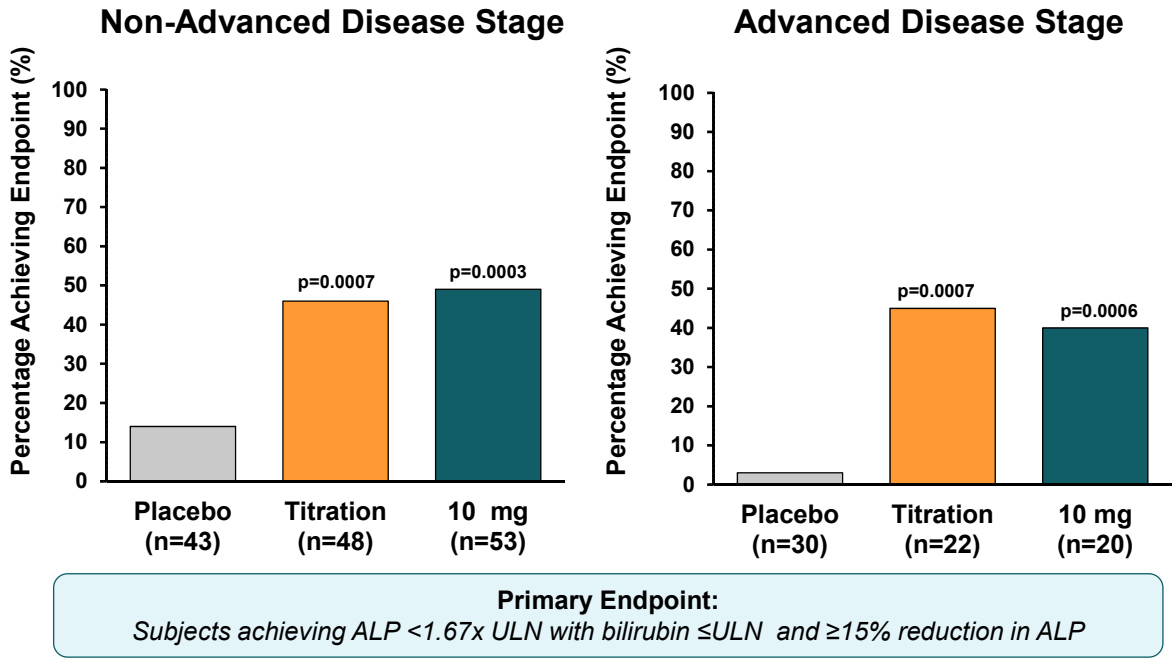
A post hoc analysis of patients from Study 747-301 with advanced PBC disease was performed based on the following criteria.

- Baseline total bilirubin >ULN
- Baseline total ALP >5X ULN
- Baseline TE >10.7 kPa
- Cirrhosis based on an initial or baseline "in study" biopsy result or patients with an Ishak score 6 (cirrhosis) or Ludwig/Scheuer PBC Stage 4
- Medical history of interest of: ascites, hepatic cirrhosis, jaundice, portal hypertension, portal hypertensive gastropathy, or varices esophageal.

A total of 30 patients in the placebo group, 22 in the OCA titration group, and 20 in the 10 mg OCA group met the criteria for advanced disease. Baseline characteristics of the advanced disease population were similar to those of the non-advanced disease stage. In addition to the criteria for advanced disease status listed above, higher levels of platelet and aminotransferases (i.e. ALT and AST) were also observed in the advanced disease groups consistent with some levels of hepatic dysfunction and hepatocellular injury.

The proportion of OCA-treated patients with advanced disease achieving the primary composite endpoint was similar to OCA-treated patients with non-advanced disease stage (Figure 29). Results of these analyses would indicate similar efficacy regardless of disease progression.

Figure 29: Percentage of Patients Achieving Primary Composite Endpoint by Disease Stage; Double-Blind, Placebo-Controlled, Phase 3 (ITT Population)



Observed data.
P-values for comparing treatments are obtained using the Cochran-Mantel-Haenszel (CMH) General Association test stratified by randomization stratification factor.

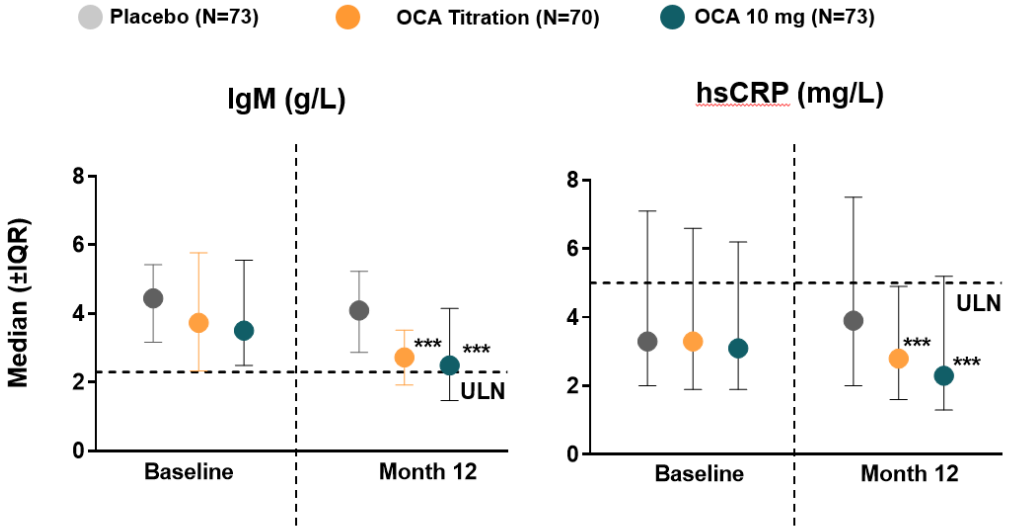
5.2.4. Markers of Immunomodulatory and Inflammatory Response

OCA treatment was associated with improvements in markers of immunomodulatory and inflammatory response compared with placebo.

In PBC, common features beyond cholestasis and presence of mitochondrial antibodies are signs of complement activation and high levels of IgM, a reflection of innate activation of the immune system as part of the disease process (Lindor 2009). CRP is an acute-phase protein synthesized by the liver in response to factors released by macrophages and adipocytes and its concentration increases in response to inflammation (Pepys 2003).

Statistically significant differences compared to placebo were observed for both OCA titration and OCA 10 mg groups for IgM (the hallmark immunoglobin increased in PBC) and hsCRP (Figure 30). Together, these findings support the immune modulatory and anti-inflammatory properties of OCA observed in preclinical studies.

Figure 30: Markers of Immunological and Inflammatory Response and Apoptosis: Median (IQR) Absolute Change from Baseline to Month 12; Phase 3 (ITT Population)



Hodges-Lehmann estimates for the median difference (OCA - Placebo).
***p<0.0001; p-value for OCA treatments to placebo was obtained using the Wilcoxon rank-sum test.

5.2.5. Non-Invasive Measures of Fibrosis

Non-invasive measurement of liver fibrosis may be useful since liver biopsies are no longer a mandatory component of PBC diagnosis or management.

Liver biopsy is no longer considered mandatory for diagnosis and management of PBC based on the AASLD and EASL guidelines (Lindor 2009, EASL 2009). According to these guidelines, patients are managed based on their biochemical status, and routine liver biopsies are no longer performed. Thus, data from liver biopsies were only collected in a small percentage of patients in the study and are, therefore, not reported.

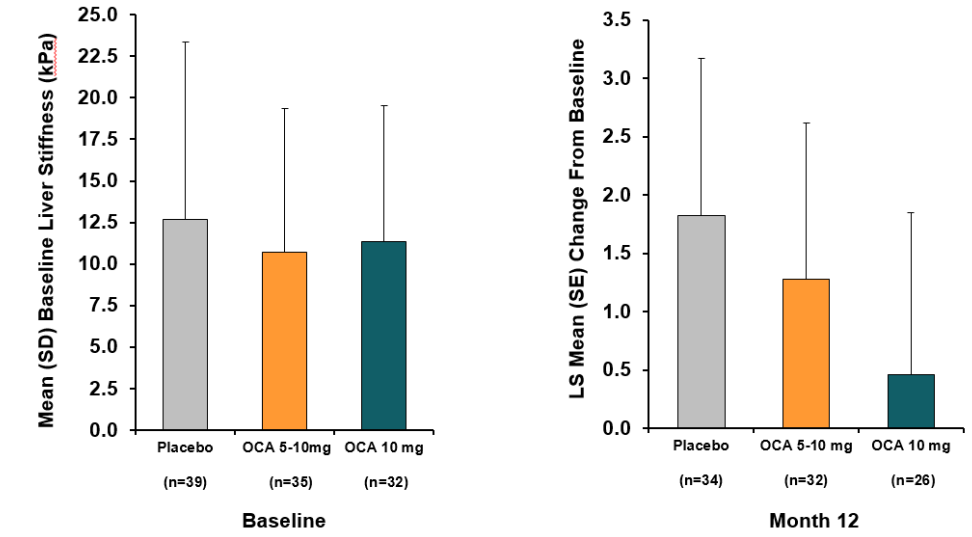
Transient elastography (Fibroscan®) is one of the best current surrogate markers of liver fibrosis in PBC (Corpechot 2012). The ELF score assesses direct serum blood markers to predict fibrosis stage in chronic liver disease (Lichtinghagen 2013).

Transient elastography was performed at a subset of sites in 92 (43%) patients using the Fibroscan transient elastography device. Following 12 months of treatment, LS mean increases in transient elastography were observed for all 3 treatment groups; however, the OCA 10 mg group has the smallest LS mean increase from Baseline, followed by the OCA titration group and then the placebo group (Figure 31).

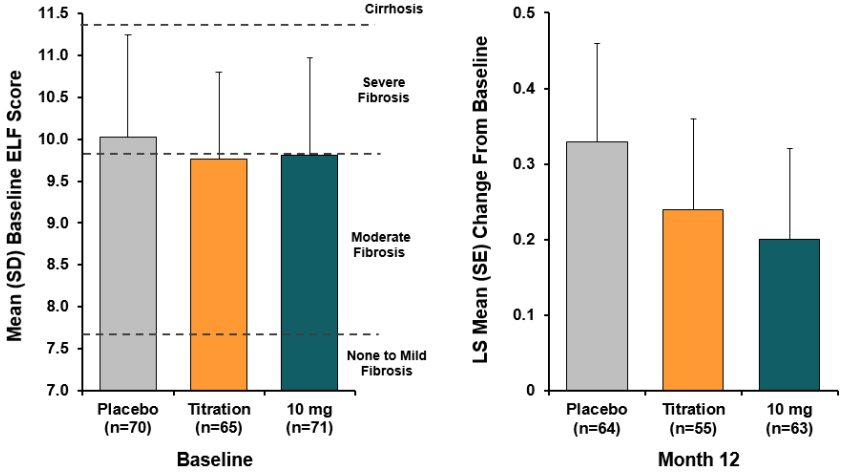
Progression of fibrosis as assessed by percentage increase in transient elastography was statistically significantly reduced in the 10 mg OCA group (2.9%) versus placebo (21.7%; $p<0.05$), but not in the OCA titration group (22.1%) (Figure 32).

Although the mean (SE) change from Baseline to Month 12 in total ELF score was not significant between placebo and OCA treatment group, the magnitude of increase in total ELF score was lower for both OCA treatment groups compared with placebo.

Figure 31: Non-Invasive Measures of Fibrosis: Transient Elastography and ELF Score; Phase 3 (ITT Population)



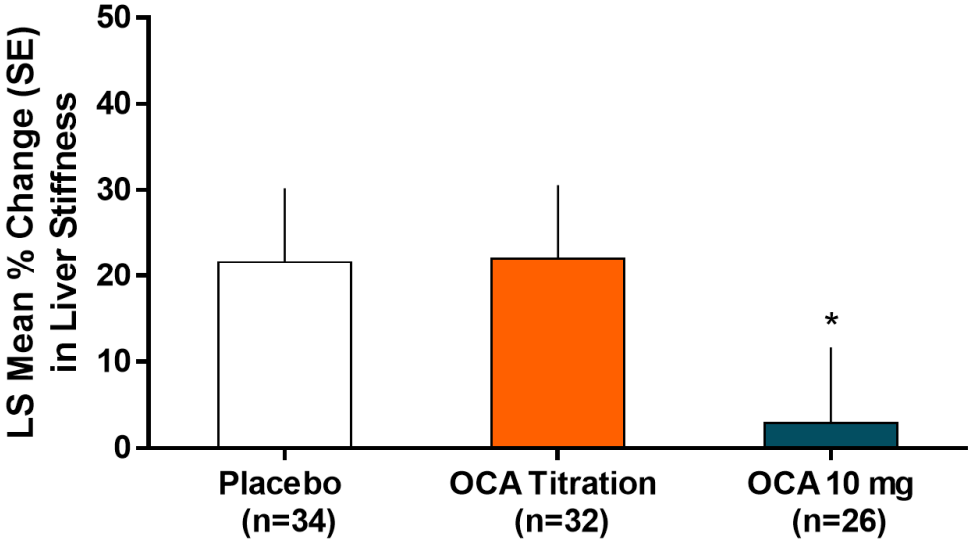
Transient elastography assessed by Fibroscan (cleared by FDA).
Fibrosis staging adapted from Corpechot et al. Hepatology. 2012; 56 (1): 198-208.



Lichtinghagen et al.
All p-values were non-significant. P-values for comparing OCA treatments to placebo were obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

Mean (SD) values at baseline and LS (SE) mean change from baseline to Month 12.
Note: Transient elastography (kilopascals [kPa]) with fibrosis ranges based on evaluation in patients with PBC by Corpechot et al (Corpechot 2012).
Note: ELF composite score with fibrosis ranges based on patients with chronic liver disease based by Lichtinghagen et al (Lichtinghagen 2013).
No p-values achieved statistical significance. p-value for comparing active treatments to placebo is obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor.

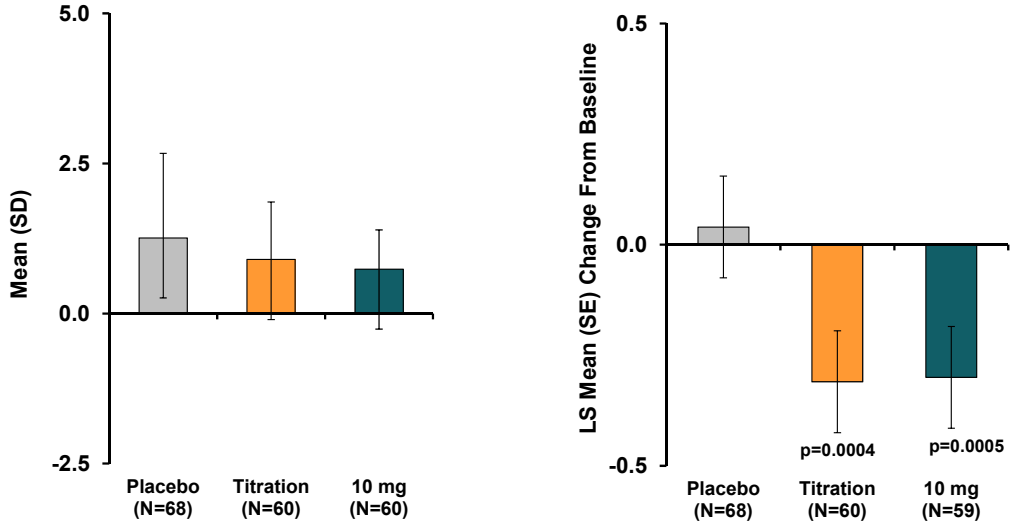
Figure 32: LS Mean % Change in Transient Elastography from Baseline (Double-Blind)



*p <0.05. p-value for comparing active treatments to placebo is obtained using ANCOVA with fixed effects for treatment, the randomization strata factor, and the baseline value as a covariate.
Note: Not all patients who received transient elastography at baseline received transient elastography at Month 12 or vice versa.

The impact of OCA on fibrosis was further evaluated using the serological based marker AST to Platelet Ratio Index (APRI; Figure 33). There was a statistically significant improvement in the LS mean APRI with both OCA titration (p = 0.0004) and 10 mg (p = 0.0005) after 12 months of treatment. In contrast, there was generally no change in this marker of fibrosis with placebo. Notably, the OCA-related improvements in APRI observed at Month 12 were sustained through 2 years of treatment. Further, patients originally randomized to placebo also saw an improvement in APRI after transitioning to OCA.

Figure 33: AST to Platelet Ratio Index (APRI); Phase 3 (ITT Population)



An APRI >0.54 is an independent predictor of liver transplant/death in PBC patients (Trivedi 2014).

5.2.6. Clinical Outcomes

The incidence of clinical outcomes associated with PBC disease progression in the Phase 3 study was expected to be low since most patients were earlier in disease stage and given the relatively short duration of the study. The pre-determined events that were used retrospectively to define a clinical outcome in Study 747-301 were:

- Death (all-cause)
- Liver transplant
- MELD score ≥15 at 2 consecutive visits
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

These events were not adjudicated by an independent committee as is standard for clinical outcomes trials that prospectively collect clinical outcomes. Using these retrospectively defined criteria, a total of 3 (4%) placebo-treated patients had 5 clinical outcomes and 3 (2%) OCA-treated patients had 4 clinical outcomes (Table 7).

Table 7: Clinical Outcomes; Double-Blind, Placebo-Controlled, Phase 3 (ITT Population)

	Placebo N = 73	OCA Treatment[a] N = 143
Overall Number of Patients with Clinical Outcomes n (%) [b]	3 (4)	3 (2)
MELD ≥15 and Baseline <12 at 2 Consecutive Visits[c], n	2	0
Other Clinical Outcomes (Number of Patients n (%) / Number of Outcomes)		
Upper GI bleeding	1/1	1/1[d]
Esophageal varices	1/2	0
Ascites/diuretic-resistant ascites	0	1/1
Hepatic encephalopathy	0	1/1
Death	0	1/1

MELD = Model for End Stage Liver Disease
[a] Data pooled from Titration OCA and 10 mg OCA treatment groups.
[b] Individual patients who reported more than one event was counted once for the overall percentage of patients.
[c] Only MELD scores are counted in patients who had at least 2 consecutive MELD scores ≥15 and baseline <12.
[d] Upper GI bleeding due to erosive / gastric ulcer.

Expected clinical outcome events per 100 patient years exposure for patients enrolled in the Phase 3 study were approximated based on the Global PBC Study Group database to be 3 events per 100 patient years. Based on this assessment, 2.2 and 4.2 events were expected to occur in the placebo and pooled OCA treatment groups, respectively, during the double-blind 12-month phase of the study. However, there were only 3 such events in the combined OCA treatment groups. In comparison, there were 3 events in the placebo group, which was slightly higher than predicted based on the Global PBC Study Group database. While no conclusion may be drawn given the small sample, this trend is encouraging if replicated in the ongoing Phase 3b clinical outcomes Study 747-302 to confirm OCA's clinical benefit in patients with PBC.

The ongoing longer term Phase 3b PBC clinical outcomes study is enrolling more advanced stage patients to enrich for accrual of events and to allow for a robust assessment of the effect of OCA on clinical outcomes that will be appropriately adjudicated.

5.2.7. Durability of OCA Treatment Effect

The treatment effect of OCA was durable during the LTSE periods of the Phase 2 and Phase 3 studies. This durability of response is a notable feature of OCA given the chronic progressive nature of PBC.

A total of 299 patients (200 patients who were randomized to OCA during the double-blind phase and 99 patients who were randomized to placebo during the double-blind phase) from the double-blind studies enrolled and were treated with OCA in the long-term extension phase (LTSE). In addition, 27 patients were enrolled and received investigational product in a short-term (8-week) open-label study.

Total OCA exposure was up to 5.0, 1.8, and 2.5 years for the open-label LTSE phases of Studies 747-201, 747-202, and 747-301, respectively.

Overall, 69% of patients enrolled in the open-label uncontrolled studies remained in the studies at the time of the 120-day safety data-cut. Two year completion rates were similar between groups receiving >5 mg to ≤10 mg OCA and those receiving >10 mg OCA. 747-202 LTSE was stopped after all patients had received at least 1 year of open-label treatment.

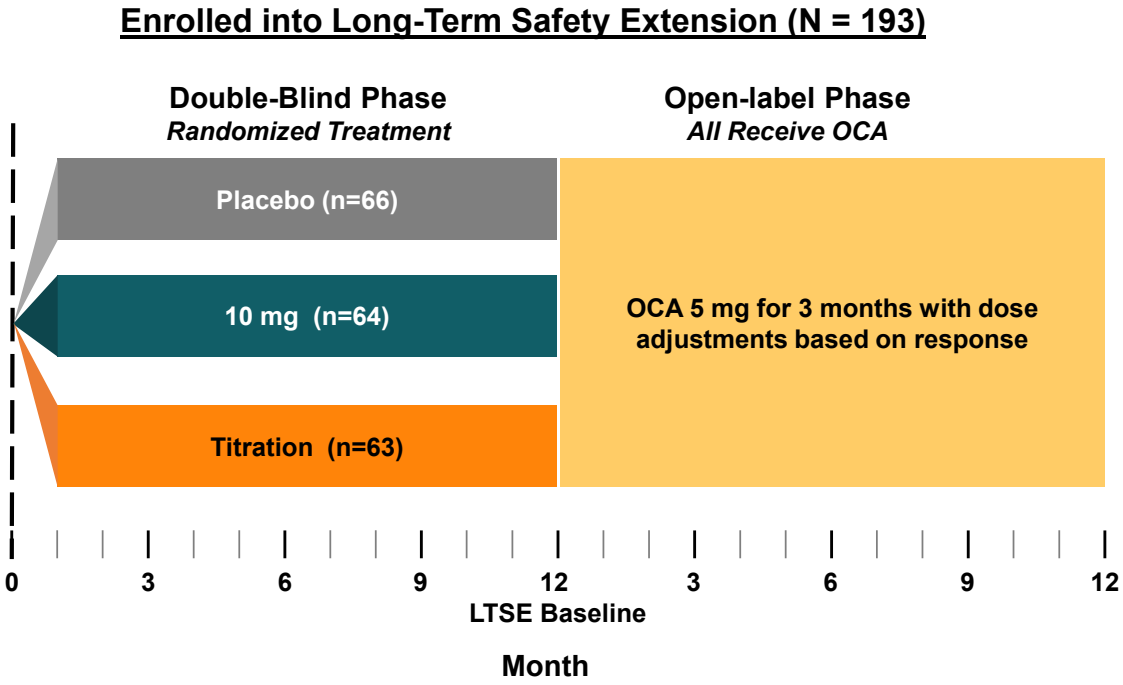
The therapeutic response observed during the 3-month, double-blind period of Studies 747-201 and 747-202 was generally maintained during the LTSE phase of both studies. Given the variability in gaps between the double-blind and LTSE phases of Studies 747-201 and 747-202, this section focuses primarily on the LTSE phase of Study 747-301, wherein patients enrolled into the LTSE phase at the double-blind Month 12 visit (total OCA exposure was up to 2.5 years).

LTSE of 747-301

The efficacy profile observed in the 12-month double-blind treatment period in patients treated with OCA remained durable over the initial 18 months of the LTSE period (total of 30 months). For patients who received placebo during the double-blind period, similar responses were observed after initiating open-label OCA during the extension.

Patients were eligible to participate in the LTSE regardless of the treatment group they were assigned to during the double-blind period. All patients who elected to participate in the LTSE started at an initial dose of OCA 5 mg. After 3 months, doses up to 25 mg were permitted in the LTSE. Patients who had a clinically significant therapeutic response during the open-label LTSE could have had their UDCA withdrawn if determined clinically appropriate by the Investigator.

Figure 34: Study Design of Open-Label, Long-Term, Safety Extension; Phase 3



In order to evaluate the durability of the response seen in OCA-treated patients from the double-blind phase, as well as to evaluate the response of patients who received placebo during the double-blind phase, data for Study 747-301 are presented by double-blind randomized treatment. Given the flexibility allowed in dose adjustments, in particular earlier in the clinical development program where patients could titrate to OCA doses >10 mg, data are summarized for the subset of patients (N = 155) from each randomized treatment arm who received a weighted average daily dose of OCA ≤10 mg (ie, OCA 5 mg and 10 mg are the proposed marketing doses). Weighted average daily dose is defined as the sum of (dose [mg] x number of days at specified dose)/total number of days on OCA. This is summarized in Table 8.

Table 8: Number of Patients Who Received a Weighted Average Daily Dose ≤10 mg

Study 747-301	Number of Patients			
	Placebo	OCA Titration	OCA 10 mg	Total
Randomized, Double-Blind Treatment	73	70	73	216
Enrolled into LTSE Phase and Received Open-Label OCA	66	63	64	193
Subset of Patients who Enrolled into the LTSE who Received a Weighted Average Daily OCA Dose of ≤10 mg	51	50	54	155

LTSE = long-term safety extension
Weighted average daily dose is defined as the sum of (dose [mg] x number of days at specified dose)/total number of days on OCA.

Table 9 summarizes the number of patients receiving a weighted average daily dose of OCA ≤10 mg by LTSE visit based on the 120-day Safety Update data cut. A total of 45 patients from the OCA titration group and 50 patients from the OCA 10 mg group had efficacy assessments for a total of 30 months (2.5 years), which included 12 months of double-blind treatment and 18 months of open-label treatment. A total of 41 patients from the placebo group had efficacy assessments for 18 months (1.5 years) of open-label OCA treatment. Key long-term efficacy data is summarized in the following sections.

Table 9: Treatment Sample Size by LTSE Visit: Safety Population, Weighted Average Daily Dose ≤10 mg, Study 747-301 (N = 155)

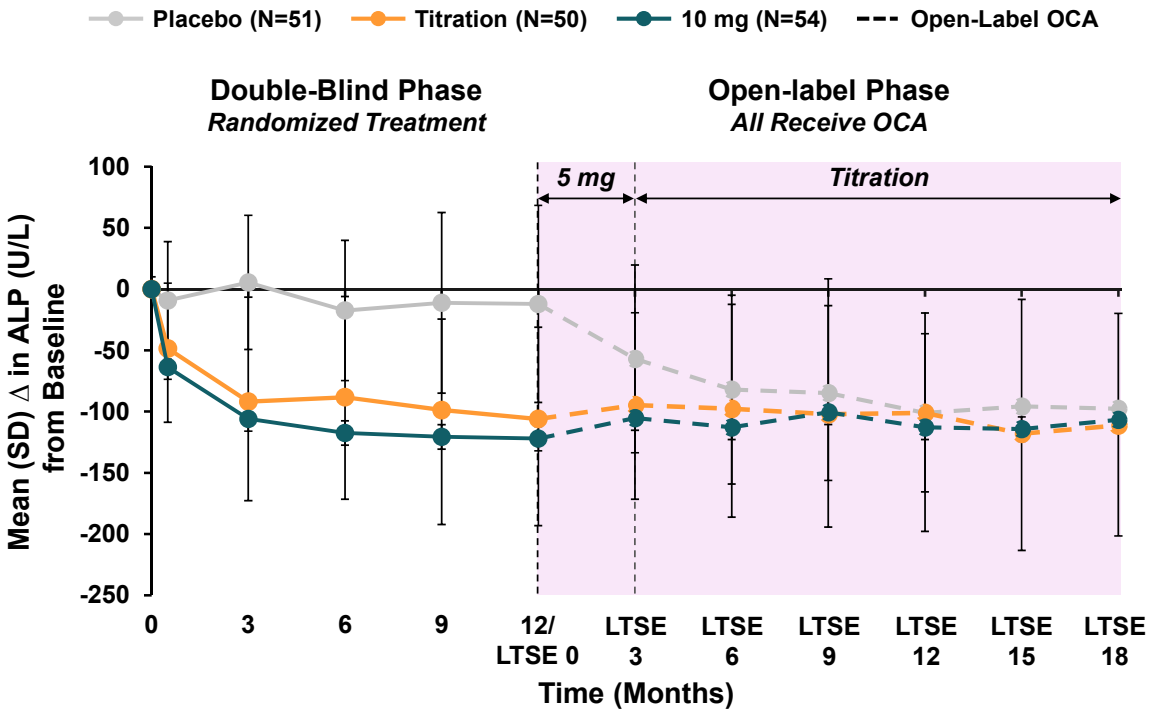
	LTSE (Open-Label OCA Weighted Average Daily Dose ≤10 mg)						
Double-Blind Randomized Treatment	**Day 0[a]**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**
Placebo	51	49	45	44	44	42	41
OCA Titration	50	50	49	49	47	44	45
OCA 10 mg	54	54	49	51	49	48	50

LTSE = long-term safety extension
[a] Month 12 visit of double-blind phase.
Data are based on a 29 Jun 2015 (120-Day Safety Update data cut).

ALP and Total Bilirubin

Mean (SE) ALP data over a 30-month treatment period (12 months double-blind and 18 months open-label) are summarized in Figure 35 for patients from Study 747-301 who enrolled into the LTSE phase. These data show substantial reductions in ALP from Month 3 that were maintained throughout a 2.5-year period. Patients originally treated with placebo in the double-blind phase achieved changes in ALP during the LTSE period that were comparable to those observed for patients continuously treated with OCA. These data are further supported by the 2-year completer population data cut for the 120-Day Safety Update, which included 104 patients who received OCA at a weighted average daily dose ≤10 mg for at least 2 years.

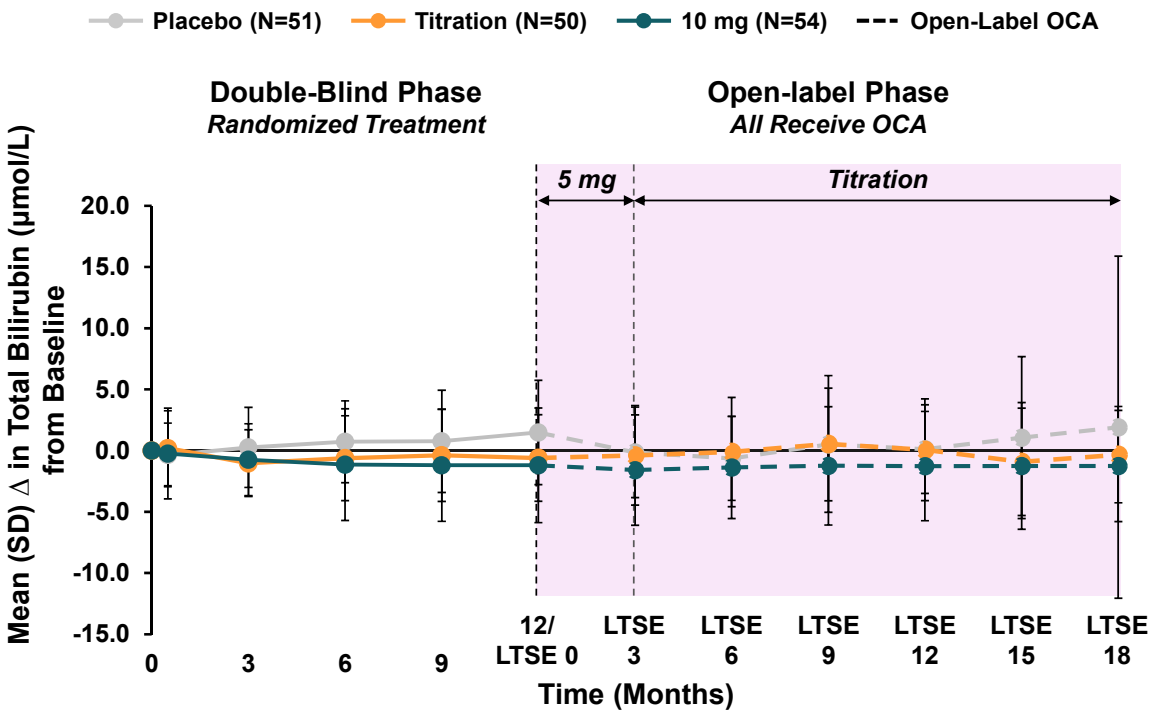
Figure 35: ALP Mean (SD) Change from Baseline Based on Double-Blind Randomized Treatment: LTSE Phase of 747-301 Safety Population (N = 155), Weighted Average Daily Dose ≤10 mg



ALP = alkaline phosphatase; LTSE = long-term safety extension
To maintain study blind, all patients started the LTSE phase at the OCA 5 mg dose. Following LTSE Month 3, OCA doses could be titrated as clinically indicated at a frequency of no more than one up-titration every 3 months.
Data are summarized by double-blind randomized treatment for those patients who had a weighted average daily OCA dose ≤10 mg across the 30-month treatment period.
Data based on 120-Day Safety Data cut (29 June 2015).

Mean total bilirubin data over a 24-month treatment period (12 months double-blind and 12 months open-label) are presented in Figure 36 for patients who enrolled into the LTSE of Study 747-301. These longer-term bilirubin data provide a clinically relevant context since bilirubin is not elevated until late in the disease. For patients who received placebo in the double-blind phase, bilirubin levels increased during the double-blind, 12-month period but showed a rapid decrease after starting open-label OCA. These results are clinically meaningful given that improvements in bilirubin, when within the normal range, have been found to have prognostic utility (Lammers 2014). The data are further supported by the 120-Day Safety Update data 2-year completer population (ie, n =104 patients who received OCA at a weighted average daily dose of ≤10 mg for at least 2 years).

Figure 36: Total Bilirubin Mean (SD) Change from Baseline Over Time by Randomized Dose: LTSE Phase of Study 747-301, Safety Population (N = 155), OCA Weighted Average Daily Dose ≤10 mg



OCA = obeticholic acid; LTSE = long-term safety extension; SD = standard deviation
To maintain study blind, all patients started the LTSE phase at the OCA 5 mg dose. Following LTSE Month 3, OCA doses could be titrated as clinically indicated at a frequency of no more than one up-titration every 3 months.
Data are summarized by double-blind randomized treatment for those patients who had a weighted average daily OCA dose ≤10 mg across the 30-month treatment period.
Data based on 120-Day Safety Data cut (29 June 2015).

5.3. Efficacy Summary

In summary, the pivotal study demonstrated clinically meaningful improvement in the primary composite endpoint shown to be associated with clinical benefit. Clinically meaningful and statistically significant improvements were also observed in markers of cholestasis, hepatic function, and hepatobiliary damage. Improvements in IgM and CRP values, contemporaneous with the improvements in liver biochemistries associated with OCA-mediated effects on bile acid homeostasis, suggest a disease-modifying effect of FXR agonism over a 12-month period. Finally, the effect of OCA was durable over 2.5 years.

6. CLINICAL SAFETY IN PBC

The OCA safety database is based on clinical pharmacology studies; 4 studies in patients with PBC, including 3 randomized, placebo controlled safety and efficacy, and studies in patients with other underlying diseases.

6.1. Features of Safety Population and Extent of Exposure

6.1.1. Extent of Exposure

Over 1600 subjects have received at least one dose of OCA.

Over 1600 male and female subjects have been exposed to at least a single dose of OCA (Table 10). This includes exposure in healthy volunteers, patients with PBC, and other indications.

Table 10: OCA Exposure

Category	Number of Subjects
Total number of subjects exposed	**>1600**
Clinical pharmacology studies conducted by Intercept and the Sponsor's partner Sumitomo Dainippon Pharma	844
Intercept clinical studies in PBC	432
Intercept sponsored studies for other indications	74
Unblinded ongoing and completed Investigator or partner initiated Studies	305

Data based on 120-Day Safety Data cut (29 June 2015).

OCA Dosing in PBC Patients

A total of 432 with PBC have been treated with OCA, 155 patients with at least 2 years of exposure, and 14 patients with at least 5 years of exposure. In PBC there has been 675 patient years of OCA exposure.

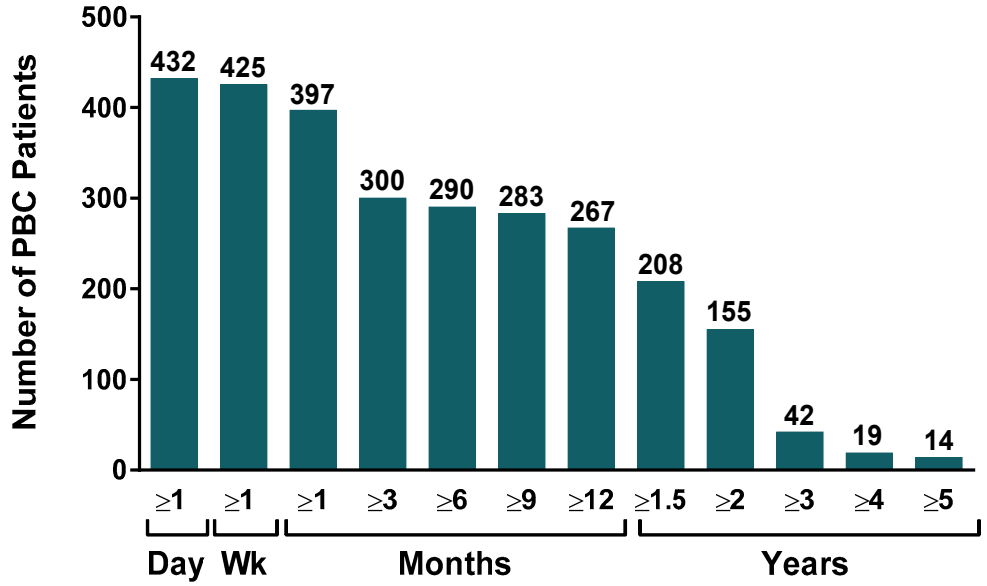
The 3 double-blind placebo-controlled studies in PBC (747-201, 747-202, and 747-301) have each been followed by open-label LTSE phases. Additionally, 1 study in PBC only consists of open-label treatment (747-205) and is not preceded by a double-blind placebo controlled phase.

Overall, during the course of the double-blind, placebo-controlled and open-label studies, a total of 432 patients with PBC have received OCA for 675 patient exposure years. PBC OCA patient exposure is summarized in Figure 37. A total of 267 (62%) patients (including double-blind, and open-label phases) have received OCA for at least 12 months and 155 (36%) patients for ≥2 years. Fourteen (3%) patients have received at least 5 years of OCA exposure.

Exposure information in patients with PBC broken out by double-blind and open-label phases is as follows:

- During the double-blind Phase 2 and 3 studies, 306 patients received at least 1 dose of OCA (mean daily dose of OCA was 18.0 mg [range 5 mg to 50 mg]) for a total of 163 patient exposure years.
- During the PBC open-label phases (747-201 LTSE, 747-202 LTSE, 747-301 LTSE, and 747-205), a total of 326 patients received at least 1 dose of OCA. Of those, almost 90% of patients had at least 6 months (279 [86%]) exposure and almost 80% (254 [78%]) of patients had at least 1 year of open-label OCA exposure.

Figure 37: OCA Exposure in Patients with PBC by Time Interval



6.2. Overall Safety Profile Across Phase 2 and Phase 3 Studies

In patients with PBC, OCA was generally safe and well tolerated including, with long-term exposure.

The most common AE was dose-dependent pruritus, which was generally mild to moderate in severity.

During the Phase 2 and 3 studies, the rate of OCA-treated patients reporting pruritus was higher in the OCA treatment groups and appeared to be dose-dependent.

With the exception of pruritus, the rates of common AEs observed with OCA treatment were generally similar across different dose groups, and few AEs occurred at a rate that was notably higher than that observed in placebo.

The majority (>80%) of patients within each study completed the double-blind phase, with a higher completion rate in the Phase 3 study.

The most common reason for withdrawal was pruritus.

6.3. Adverse Drug Reactions

The most frequently observed adverse drug reactions (ADRs) were pruritus/skin eruptions, fatigue/tiredness, abdominal pain and discomfort. None of the ADRs were serious.

The adverse drug reactions (ADRs) identified in the double-blind, Phase 3 study are presented in Table 11. ADRs are defined as an event occurring in ≥5% in either OCA treatment group and at a rate that was ≥1% than that observed in the placebo group.

Table 11: Adverse Drug Reactions (Double-Blind, Placebo-Controlled Phase 3 Study, Safety Population [N = 216])

Adverse Reaction[a] n (%)	Placebo (N = 73)	OCA Titration[h] (N = 70)	OCA 10 mg (N = 73)
Pruritus/Skin eruptions[b]	28 (38)	39 (56)	51 (70)
Fatigue/Tiredness[c]	11 (15)	13 (19)	18 (25)
Abdominal pain and Discomfort[d]	10 (14)	13 (19)	7 (10)
Rash and Urticaria[e]	6 (8)	5 (7)	7 (10)
Oropharyngeal pain	1 (1)	5 (7)	6 (8)
Dizziness[f]	4 (5)	5 (7)	5 (7)
Constipation	4 (5)	5 (7)	5 (7)
Arthralgia	3 (4)	4 (6)	7 (10)
Cough	5 (7)	4 (6)	6 (8)
Thyroid function abnormality[g]	2 (3)	4 (6)	3 (4)
Eczema	0	4 (6)	2 (3)
Procedural pain	1 (1)	4 (6)	1 (1)
Edema peripheral	2 (3)	2 (3)	5 (7)
Palpitations	1 (1)	2 (3)	5 (7)
Pyrexia	1 (1)	0	5 (7)

[a] ADRs were defined as adverse events that occurred in ≥5% in either OCA treatment group and occurring ≥1% more than placebo.
[b] Includes Prurigo, Pruritus, Pruritus generalised, Ear pruritus, Eye pruritus, Anal pruritus, Vulvovaginal pruritus, and Rash pruritic
[c] Includes Fatigue and Asthenia
[d] Includes Abdominal pain upper, Abdominal pain, Abdominal discomfort, Abdominal pain lower, Abdominal tenderness, and gastrointestinal pain.
[e] Includes Rash, Rash macular, Rash papular, Rash maculo-papular, Heat rash, Urticaria cholinergic, Urticaria
[f] Includes Dizziness, Syncope, Presyncope
[g] Includes Thyroxine free decreased, Blood thyroid stimulating hormone increased, Hypothyroidism
[h] Patients randomized to OCA titration received OCA 5 mg for the initial 6 month period. At Month 6, patients who did not achieve the composite endpoint and did not have evidence of tolerability issues were titrated from 5 mg to 10 mg for the final 6 months of the double blind phase.

6.4. Discontinuation Due to an Adverse Event

More than 90% of patients completed the double-blind phase of the Phase 3 study; 98% to 100% of OCA-treated patients who completed the study enrolled into the LTSE. The 5 mg→10 mg titration strategy resulted in lower patient discontinuations rates relative to higher doses.

In the double-blind, placebo-controlled, Phase 3 study, 3 patients (4%) in the placebo group, 5 patients (7%) in the OCA titration group, and 8 patients (11%) in the OCA 10 mg group experienced AEs leading to study drug withdrawal or study discontinuation Table 12.

The majority of AEs leading to study discontinuation were due to pruritus. Discontinuation rates for other AEs were not obviously different between the OCA and placebo groups.

Table 12: Adverse Events Leading to Study Drug Withdrawal or Study Discontinuation (Double-Blind, Placebo-Controlled Phase 3 Study, Safety Population [N = 216])

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
Preferred Term	**n (%)[a]**	**n(%)[a]**	**n (%)[a]**
Patients with AEs leading to Study Drug Withdrawal or Study Discontinuation	3 (4)	5 (7)	8 (11)[b]
Pruritus	0	1 (1)	7 (10)
Diarrhoea	0	1 (1)	0
Cardiac failure	0	1 (1)	0
Hallucination	0	1 (1)	0
Interstitial lung disease	0	1 (1)	0
Contusion	0	0	1 (1)
Rash	1 (1)	0	0
Abdominal distension	1 (1)	0	0
Nausea	1 (1)	0	0
Vomiting	1 (1)	0	0
Headache	1 (1)	0	0
Osteoarthritis	1 (1)	0	0

[a] A treatment-emergent adverse event is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug.
[b] Patient 146003 (OCA 10 mg) experienced an AE of fatigue, which was recorded as a discontinuation on the AE eCRF, however the patient remained in the study and study drug was not changed and has not been included.
Note: At each level of summation (overall, preferred term), patients reporting more than one AE are counted only once per dose group.

6.5. Serious Adverse Events

None of the SAEs were assessed by the Investigators as related to study drug. There was no dose effect and no pattern in the types of events that occurred.

In the Phase 3 study, the incidence of SAEs was 11 patients (16%) in the OCA titration group, 8 patients [11%] in the OCA 10 mg treatment group, and 3 patients [4%] in the placebo group (Table 13). None of the SAEs were assessed by the Investigator as related to study drug. There was no discernable trend in the types of SAEs that occurred in patients treated with OCA. These events predominantly occurred in 1 patient each with the exception of varicose vein and osteoarthritis, which were experienced by more than 2 patients each.

In the OCA titration group, most events occurred after 6 months of treatment in patients who remained at OCA 5 mg. Aside from 1 patient who died due to worsening of preexisting cardiac failure (Section 6.6), and 1 patient with interstitial lung disease, no patients were discontinued due to the SAE. The primary body system that appeared to underpin the relatively higher incidence of SAEs in this treatment group was "Gastrointestinal Disorders" (4 patients [6%] and 1 patient [1%] in OCA titration and placebo groups, respectively). No patients in the OCA 10 mg group reported SAEs in this body system.

Conversely, in the OCA 10 mg group, the observed SAEs did not develop within a consistent timeframe and no patients were discontinued due to any of the events. The body system that primarily underpinned the relatively higher incidence of SAEs in the OCA 10 mg group was "Injury, Poisoning, and Procedural Implications" (4 patients [5%] 1 patient [1%] in placebo) and "Musculoskeletal and Connective Tissue Disorders" (3 patients [4%], none in placebo). Patients in the titration group experienced no SAEs in the "Injury, Poisoning, and Procedural Implications" system organ class (SOC) and only 1 patient (1%) experienced an SAE in the SOC of "Musculoskeletal and Connective Tissue Disorders".

Table 13: Serious Adverse Events (Double-Blind, Placebo-Controlled, Phase 3, Safety Population [N = 216])

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
System Organ Class Preferred Term	**Patients (%) Events[a]**	**Patients (%) Events[a]**	**Patients (%) Events[a]**
All Serious Adverse Events	3 (4) 8	11 (16) 15	8 (11) 11
Gastrointestinal Disorders	**1 (1) 3**	**4 (6) 4**	**0**
Ascites	0	1 (1) 1	0
Varices oesophageal	1 (1) 2	0	0
Upper gastrointestinal haemorrhage	1 (1) 1	1 (1) 1	0
Splenic artery aneurysm	0	1 (1) 1	0
Abdominal wall haematoma	0	1 (1) 1	0
Nervous System Disorders	**0**	**2 (3) 3**	**0**
Hepatic encephalopathy	0	1 (1) 2	0
Syncope	0	1 (1) 1	0
Vascular Disorders	**0**	**2 (3) 2**	**0**
Varicose vein	0	2 (3) 2	0
Cardiac Disorders	**1 (1) 1**	**1 (1) 2**	**0**
Cardiac failure	0	1 (1) 2	0
Sick sinus syndrome	1 (1) 1	0	0
General Disorders and Administration Site Conditions	**2 (3) 2**	**1 (1) 1**	**0**
Chest pain	1 (1) 1	0	0
Non-cardiac chest pain	1 (1) 1	0	0
Oedema	0	1 (1) 1	0
Infections and Infestations	**0**	**1 (1) 1**	**2 (3) 2**
Erysipelas	0	0	1 (1) 1
Parotitis	0	1 (1) 1	0
Pneumonia	0	0	1 (1) 1
Respiratory, Thoracic and Mediastinal Disorders	**1 (1) 1**	**1 (1) 1**	**0**
Dyspnoea	1 (1) 1	0	0
Interstitial lung disease	0	1 (1) 1	0

Table 13: Serious Adverse Events (Double-Blind, Placebo-Controlled, Phase 3, Safety Population [N = 216]) (Continued)

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
System Organ Class Preferred Term	**Patients (%) Events[a]**	**Patients (%) Events[a]**	**Patients (%) Events[a]**
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (1) 1**	**3 (4) 3**
Osteoarthritis	0	0	2 (3) 2
Intervertebral disc protrusion	0	0	1 (1) 1
Rotator cuff syndrome	0	1 (1) 1	0
Injury, Poisoning and Procedural Complications	**1 (1) 1**	**0**	**4 (5) 5**
Clavicle fracture	0	0	1 (1) 1
Radius fracture	0	0	1 (1) 2
Tibia fracture	1 (1) 1	0	0
Wrist fracture	0	0	1 (1) 1
Post procedural haemorrhage	0	0	1 (1) 1
Blood and Lymphatic System Disorders	**0**	**0**	**1 (1) 1**
Anaemia	0	0	1 (1) 1

[a] At each level of summation (overall, system organ class, preferred term), patients reporting more than one AE are counted only once.

6.6. Deaths

In the double-blind and LTSE Phase 3 study in patients with PBC, there were 2 deaths, neither of which were considered related to drug therapy. Both patients developed complications of their pre-existing, concomitant conditions (congestive failure and xenograft valve replacement).

One male, 82 year-old patient (OCA titration [receiving OCA 5 mg at time of death]), with a medical history of chronic kidney disease, PBC, and ischemic cardiovascular and congestive cardiac failure, died due to worsening congestive cardiac failure.

One male, 70-year old patient (OCA 10 mg) with a prosthetic biological aortic valve, died due to sepsis secondary to endocarditis. The patient's last dose prior to the event was OCA 10 mg.

Aside from the fact that both patients were males >65 years of age and treated with OCA, there were no distinct similarities between these 2 cases. Neither event was considered related by the Investigator.

6.7. Adverse Events of Special Interest

6.7.1. Pruritus

Pruritus was the most frequently observed AE. It was mild or moderate in most patients but showed a dose-related incidence. The titration approach in the Phase 3 study (5mg titrating to 10mg) significantly mitigated both the incidence and severity of pruritus, resulting in only a single patient discontinuation in the OCA titration group over 12 months of treatment.

There was a clear dose-relationship for pruritus in the Phase 2 studies (with a high discontinuation rate at 25 mg and 50 mg), with no additional efficacy at OCA doses above 10 mg. Accordingly, lower doses were evaluated in the OCA Phase 3 clinical study (5 mg and 10 mg). Titration from OCA 5 mg to 10 mg is the proposed dosing regimen for the marketed product, based on the analysis of pruritus below.

6.7.1.1. Overall Profile of Pruritus Events

In the double-blind, placebo-controlled Phase 3 study, the severity of pruritus was assessed in 2 ways:

- By physicians using a 3 part AE assessment scale: Mild, Moderate, or Severe
- By patients using a patient reported outcome (PRO) measure (the VAS)

The primary observations are as follows:

- There was a dose-related increase in the incidence of pruritus
- Most pruritus events were mild or moderate in severity and generally manageable
- Only 1 patient (1%) in the titration group discontinued from the study versus 7 patients (10%) in the OCA 10 mg treatment group demonstrating improved tolerability

In the double-blind, placebo-controlled Phase 3, 64%, 53%, and 60% of patients in the placebo, OCA titration, and OCA 10 mg treatment groups, respectively, were already experiencing pruritus at Baseline. Compared with placebo (38%), the overall incidence of treatment-emergent pruritus events was greater in the OCA titration (56%) and OCA 10 mg groups (70%) (Table 14).

Median time to onset of pruritus was found to be dose-dependent in OCA-treated patients, with earlier onset at the 10-mg dose (9 days) compared to the dose titration group (24 days), both occurring earlier than pruritus observed in the placebo group (approximately 51 days). OCA titration appeared to mitigate the first time to onset of severe pruritus events (158 days), compared with 11 days in the OCA 10 mg group (Table 14).

Table 14: On-Study Pruritus: (Double-Blind, Placebo-Controlled, Phase 3 Study, Safety Population [N = 216])

	Placebo (N = 73)	OCA Titration (N = 70)	OCA 10 mg (N = 73)
	Patients (%)	Patients (%)	Patients (%)
History of Pruritus	47 (64)	45 (64)	45 (62)
Pruritus Ongoing at Baseline	47 (64)	37 (53)	44 (60)
Patients reporting at least 1 On-Study Pruritus Event[a], n (%)	28 (38)	39 (56)	51 (70)
Patients with On-Study of Pruritus leading to Discontinuation[b]	0	1 (1)	7 (10)
Time to Onset of On-Study Pruritus			
n[b], n[c]	28, 5	39, 13	51, 17
Mean (SD) Time to First Onset	81.4 (98.72)	62.6 (82.41)	47.3 (84.53)
Median Time to First Onset	50.5	24.0	9.0
Mean (SD) Time to First Onset of Severe	102.6 (94.49)	160.2 (138.26)	46.1 (72.87)
Median Time to First Onset of Severe	75.0	158.0	11.0

Note: An on-study AE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug.

[a] Incidence is calculated using the number of patients randomized per treatment group as the denominator. Pruritus events included the MedDRA preferred terms of Pruritus, Rash pruritic, Prurigo, Pruritus generalised, Eye pruritus, Ear pruritus, Anal pruritus, and Vulvovaginal pruritus.

[b] Number of patients with event of pruritus.

[c] Number of patients with event of severe pruritus.

Source: CSR 747-301, Section 14, Table 14.3.1.17.2 and Table 14.3.1.19.1

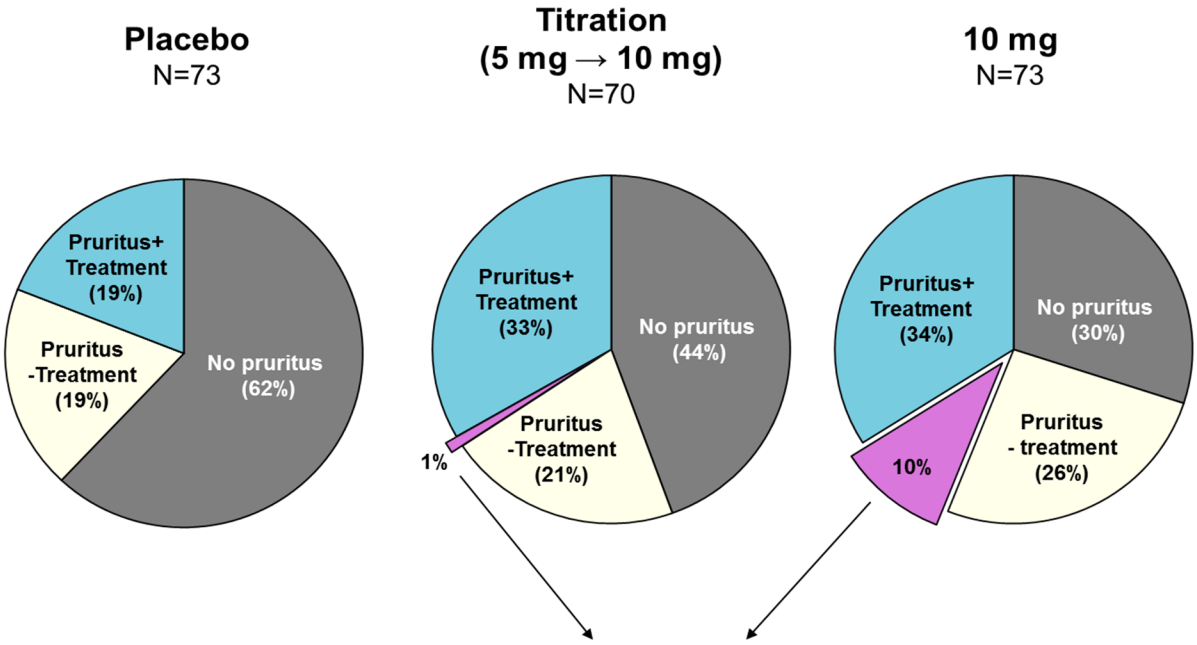
6.7.1.2. Management of Pruritus

On-study pruritus was generally manageable. A substantial number of patients in each treatment group who experienced pruritus found it tolerable and were able to remain in the study without requiring treatment.

In an effort to manage significant pruritus during the study, interventions based on AASLD guidelines were recommended to Investigators. These options included bile acids sequestrants and/or antihistamines, changes in dosing frequency, and study drug holidays. In the case of severe pruritus, patients were to be instructed to stop taking study drug until the pruritus subsided to an acceptable level at which time it should be restarted (likely, on a modified, alternate day dosing schedule). Other therapies were also accepted as clinically appropriate.

Figure 38 summarizes patients who had no on-study pruritus and those that did. Although pruritus occurred more frequently with OCA than placebo, many patients did not experience pruritus nor did they require an intervention for it. The vast majority of patients who received pruritus-treatment were able to tolerate the event, particularly in the OCA titration group.

Figure 38: Pruritus and Patient Management of Pruritus (Double-Blind, Placebo-Controlled, Phase 3 Study [Safety Population, N = 216])



Discontinued due to pruritus regardless of treatment for pruritus.

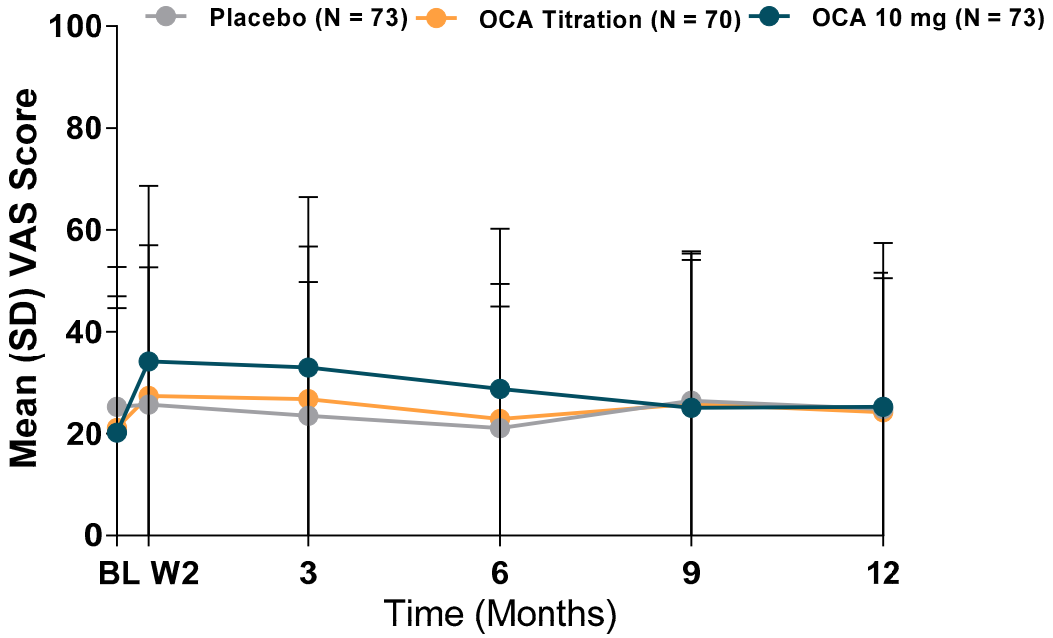
6.7.1.3. Patient Reported Outcome Pruritus Assessments

The severity of pruritus as assessed by patients using a VAS was almost identical in OCA- and placebo-treated patients after 12 months of treatment.

Pruritus is a generally subjective symptom. In order to assess the patient experience of pruritus, several patient reported outcomes tools were used. One of such measures was the VAS for pruritus. Using this tool, patients were asked to draw a vertical line through anywhere between 0 and 100 indicating the number which they felt best represented the severity of their pruritus.

Despite an early increase in pruritus severity, scores were similar in OCA- and placebo-treated patients after 12 months of treatment, suggesting that patients' perception of pruritus severity improved with continued treatment; despite an initial increase (Figure 39).

Figure 39: Patient Assessed Severity of Pruritus (Last-Observation-Carried-Forward) (Double-Blind, Placebo-Controlled, Phase 3 Study, Safety Population, N = 216])



6.7.2. Fatigue

While AEs of fatigue were reported more frequently in the OCA-treated patients in the double-blind, Phase 3 study, there was no difference between groups as assessed by the patient reported fatigue outcomes tool (PBC-40), and fatigue scores remained either unchanged or decreased over time in OCA treatment groups. No patients discontinued due to fatigue.

In the Phase 3 study, the incidence of on-study fatigue was similar in the titration and placebo groups when fatigue was assessed as an AE. Evaluation of fatigue using the PBC-40 fatigue domain scoring system demonstrated similar fatigue levels across all 3 treatment groups. Likewise, the Phase 2 data showed similar rates of on-study fatigue in the placebo and OCA treatment groups.

6.7.3. Effects on HDL-C and LDL-C

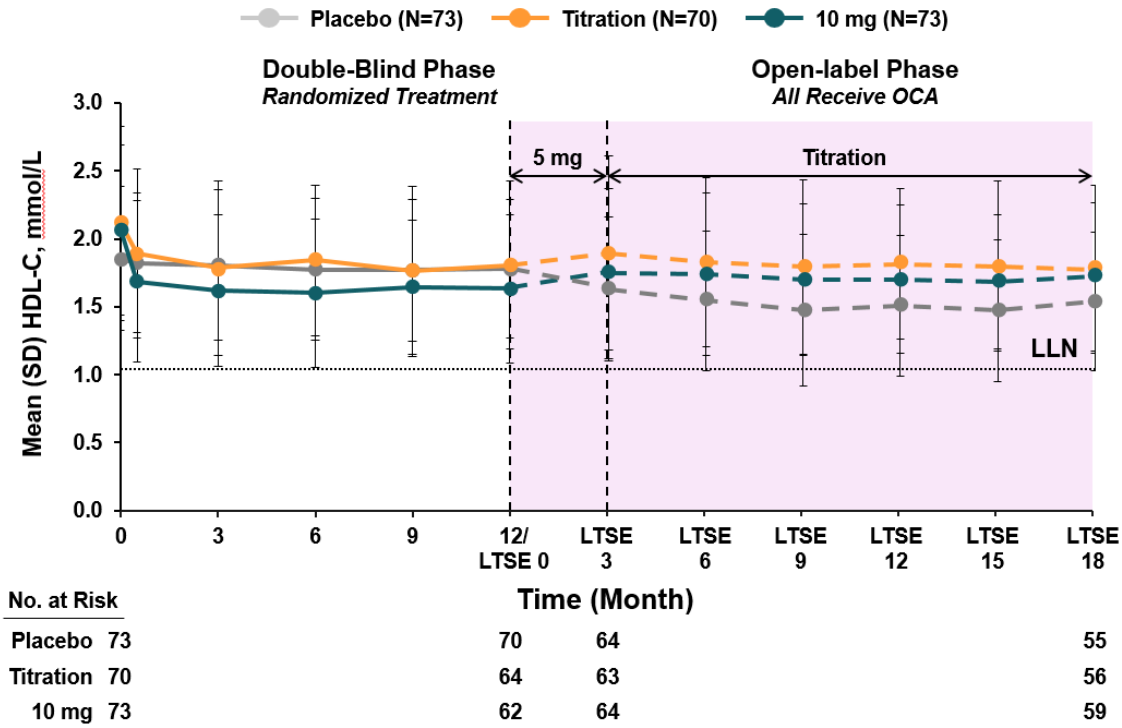
PBC is characterized by hyperlipidemia and particularly with high HDL–C levels that exceed LDL-C levels. Treatment with OCA was associated with an early and sustained small decrease in HDL-C levels; these levels remained within the normal range even with long-term treatment. Small and transient increases were observed in LDL-C levels at Week 2 in OCA-treated patients. However, levels returned to Baseline over the course of the study and were comparable with placebo at Month 12.

As expected, the majority of patients in Phase 3 Study showed elevated HDL-C levels at baseline. As Figure 40 shows, there was an early and sustained, dose-dependent decrease in HDL-C in OCA-treated patients compared with placebo.

Reductions in HDL-C were evident at Week 2 (-0.035 mmol/L [-1%], -0.204 mmol/L [-9%], and -0.412 mmol/L [-20%], in placebo, OCA titration, and OCA 10 mg groups, respectively) and remained stable. Despite these changes, the mean HDL-C levels remained stable and above the lower limit of normal in both OCA treatment groups.

Post-baseline, few OCA-treated patients (6 out of 143) fell 2 SD below the mean at any point in time during the DB phase. Of these patients, none experienced an atherosclerotic cardiovascular event.

Figure 40: Mean (SD) HDL-C Values (Double-Blind and LTSE Phase 3)

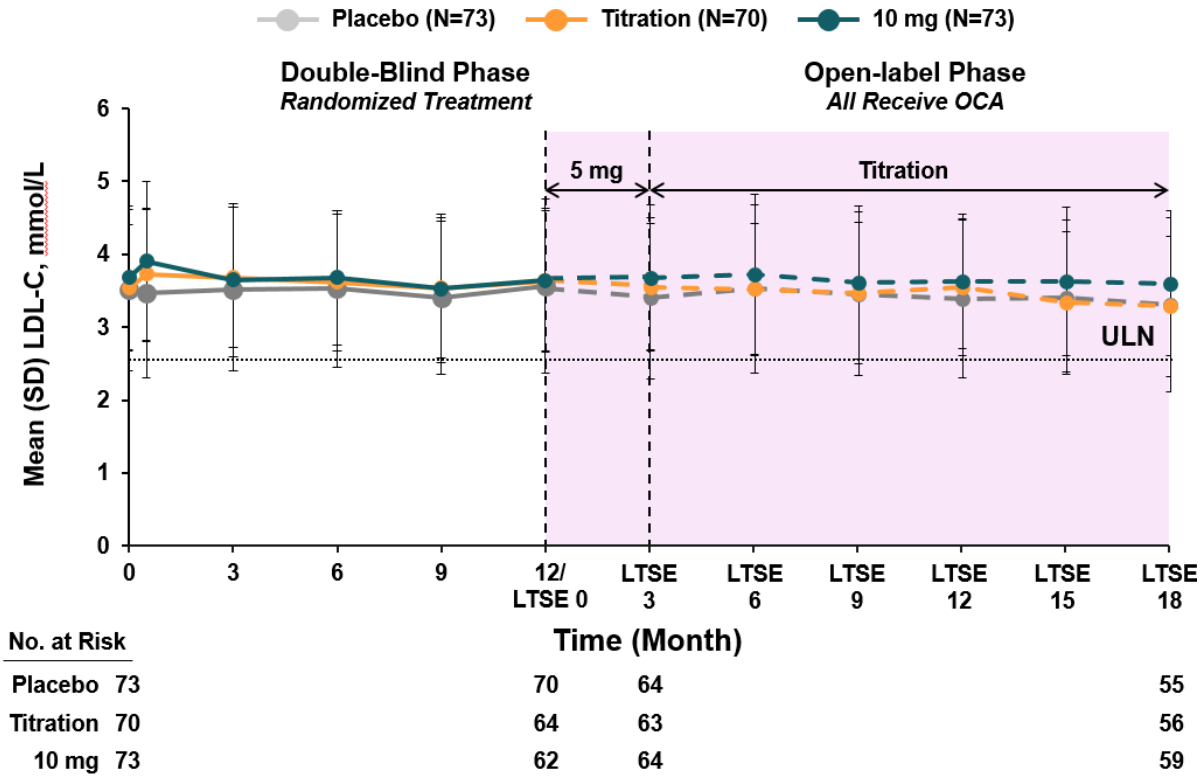


HDL = high-density lipoprotein; LLN = lower limit of normal; LTSE = long-term safety extension; OCA = obeticholic acid; SD = standard deviation. Double-blind month 12 data are presented at Month 12/LTSE 0. Data based on 120-Day Safety Data cut (29 June 2015).

Mean Baseline LDL-C levels were elevated and above the ULN for all treatment groups and remained elevated for the duration of treatment. Small increases in mean LDLc levels were observed at Week 2 (mean increase of 5.7% and 5.9% in OCA titration and OCA 10 mg-treated patients, respectively), which had essentially resolved by Month 3. A reduction of -1.1% was observed in placebo-treated patients at Week 2. At Month 12, mean LDL-C levels were increased from Baseline by 3.5%, 1.2%, and 1.9% in the OCA titration, OCA 10 mg group, and placebo groups, respectively, and absolute values were comparable to placebo (3.6 mmol/L

across all treatment groups) (Figure 41). Conversely, decreases were observed in VLDL and triglycerides in OCA-treated patients.

Figure 41: Mean (SD) LDL-C Values (Double-Blind and LTSE Phase 3)



LDL = low-density lipoprotein; LTSE = long-term safety extension; OCA = obeticholic acid; SD = standard deviation; ULN = upper limit of normal. Double-blind month 12 data are presented at Month 12/LTSE 0.
Data based on 120-Day Safety Data cut (29 June 2015).

A similar rate of serious cardiovascular events has been observed in OCA and placebo-treated patients.

In the double-blind, placebo-controlled, Phase 3 study, the rate of serious cardiovascular AEs was the same in OCA titration and placebo-treated patients (1 patient [cardiac failure, OCA titration], 1 patient [sick sinus syndrome, placebo]). No patients experienced cardiovascular SAEs in the OCA 10 mg group.

During the LTSE of this study, 2 additional patients experienced cardiovascular SAEs (1 patient with a pre-existing prosthetic valve experienced multiple complications that were fatal: aortic valve stenosis, ventricular fibrillation, and cardiac failure [discussed in Section 6.6], and 1 patient experienced a splenic infarct).

The long-term cardiovascular implications of OCA treatment, if any, continue to be investigated in the ongoing LTSE studies and the long-term PBC outcomes study including an adjudication of cardiovascular events.

6.8. Other Safety Considerations

6.8.1. Clinical Laboratory Measures

Other than the changes described above, no clinically meaningful changes have been noted in hematology and chemistry assessments.

6.8.2. Hepatic Safety

The incidence of hepatic adverse events was similar across OCA and placebo groups in the Phase 3 study with a pattern consistent with those associated with late stage chronic liver disease. Across the pooled Phase 2 and 3 PBC studies, a small number of OCA-treated PBC patients experienced hepatic events considered to be adverse reactions, primarily at higher doses.

In the Phase 3 study, the incidence of hepatic AEs including events typically associated with decompensated liver disease (eg, ascites, hepatic encephalopathy, esophageal varices), was similar across all treatment groups (Table 15).

Table 15: Hepatic Adverse Events (Double-Blind, Placebo-Controlled, Phase 3 Study, Safety Population [N = 216])

n (%)	Placebo (N = 73)	OCA Titration[a] (N = 70)	OCA 10 mg (N = 73)
Hepatic Adverse Events (total)	1 (1)	2 (3)	1 (1)
Ascites	0	1 (1)	1 (1)
Esophageal Varices	1 (1)	1 (1)	0
Hepatic Encephalopathy	0	1 (1)	0

Note: Events include both serious and non-serious adverse events. At each level of summation (overall, preferred term), patients reporting more than one TEAE are counted only once per dose group
[a] 5 mg titrated to 10 mg after 6 months based on response and tolerability.

In the Phase 3 study, increases in AST, ALT, or bilirubin occurred in a small minority of OCA treated patients, but notably fewer than the number of placebo patients with such increases in liver biochemistries.

The majority of OCA treated patients in the Phase 3 study experienced improvements in liver biochemistries while placebo treated patients generally deteriorated or remained at significantly elevated levels. Overall, the incidence of elevated liver biochemistries was lower with OCA compared with placebo (Table 16).

Table 16: Liver Biochemical Tests (Double-Blind, Placebo-Controlled, Phase 3 Study, Safety Population [N = 216])

n (%)	Placebo (N = 73)	Titration[a] (N = 70)	10 mg (N = 73)
Liver Biochemical Tests (total)	9 (12)	6 (9)	2 (3)
AST >2x baseline and/or ALT >2x baseline	2 (3)	1 (1)	1 (1)
AST >2x baseline and/or ALT >2x baseline and Total Bilirubin > 2x baseline	0	0	0
AST >5x ULN and/or ALT >5x ULN	9 (12)	5 (7)	1 (1)
AST >3X ULN and/or ALT >3x ULN and Total Bilirubin >2x ULN	1 (1)	0	1 (1)

Note: Baseline is the average of all visit values prior the first dose in the double-blind phase. If result from only 1 evaluation are available, the available data from this evaluation is used as the baseline value. Post-baseline visits include scheduled and unscheduled visits after initiation of study drug.
Categories are not mutually exclusive.
[a] 5 mg titrated to 10 mg after 6 months based on response and tolerability

In a pooled, blinded and independent analysis of data from the Phase 2 and Phase 3 studies by a hepatic safety adjudication committee, one case of a hepatic adverse reaction was identified in the OCA 10 mg group (<1%) and one in the placebo (<1%) group. None were identified in the OCA titration group. Incidence rates were higher with higher doses (1 [2%] patient with 25 mg OCA and 2 [4%] patients with 50 mg OCA).

6.8.2.1. Advanced Disease Population

Safety was also evaluated in patients with advanced disease (Table 17) (see definition of advanced disease in Section 5.2.3). The overall frequency of AEs including pruritus were similar in advanced and non-advanced disease and across treatment groups. However, discontinuation rates due to pruritus were higher in the advanced disease group. At the maximum dose (OCA 10 mg), SAE rates were comparable between the 2 subgroups. However, in the OCA titration group, the rate of SAEs appeared to be higher in the advanced disease versus non-advanced populations. These SAEs were primarily underpinned by events in the "Gastrointestinal Disorder" SOC. No patients experienced such SAEs in the OCA 10 mg group. This suggest that the incidence of such SAEs, which could be associated with decompensated disease, do not appear to be dose-dependent. Otherwise, similar to the overall population and the non-advanced sub-group, no distinct pattern was observed in the types of SAEs that occurred in the advanced disease OCA-treated patients.

Table 17: AE Profile of Patients with Advanced Versus Non-Advanced Disease (Double-Blind, Placebo-Controlled, Phase 3; Safety Population [N = 216])

	Advanced Disease			Non-Advanced Disease		
n, (%)	Placebo N = 30	OCA titration N = 22	OCA 10 mg N = 20	Placebo N = 43	OCA titration N = 48	OCA 10 mg N = 53
All AE	27 (90)	22 (100)	18 (90)	39 (91)	43 (90)	51 (96)
Most Common AE (Pruritus)	7 (23)	12 (55)	15 (75)	21 (49)	27 (56)	35 (66)
Severe Pruritus	2 (7)	4 (18)	7 (35)	3 (7)	9 (19)	10 (19)
SAEs	1 (3)	6 (27)	2 (10)	2 (5)	5 (10)	6 (11)
Withdrawal due to AE	2 (7)	3 (14)	5 (25)	1 (2)	2 (4)	3 (6)a
Withdrawal due to pruritus	0	0	5 (25)	0	1 (2)	2 (4)
Death	0	1 (5)	0	0	0	0
Completed Double-Blind	28 (93)	19 (86)	15 (75)	42 (98)	45 (94)	49 (92)
Enrolled into LTSE	28 (93)	19 (86)	15 (75)	38 (88)	44 (92)	49 (92)

[a] Patient 146003 (OCA 10 mg) experienced an AE of fatigue, which was recorded as a discontinuation on the AE eCRF; however the patient remained in the study and study drug was not changed and has not been included.
Note: At each level of summation (overall, preferred term), patients reporting more than one AE are counted only once per dose group.

6.9. Current Treatment Options

Ursodeoxycholic acid (UDCA) is the only medicine currently approved to treat PBC, but up to 70% of UDCA-treated patients either fail to respond or have a suboptimal response.

Up to 70% of UDCA-treated patients either fail to respond or have a suboptimal response, with higher rates of suboptimal response observed in patients diagnosed at younger ages. Despite near universal use of UDCA, 44% of UDCA-treated patients progress to liver transplant or death over 5, 10, and 15 years (Lammers 2014). In such patients, liver transplant is the only available salvage therapy. A significant unmet medical need remains for new therapies that provide additional improvement to UDCA or in patients unable to tolerate UDCA.

6.10. Relationships of Safety Findings to Treatment Duration

Long-term treatment with OCA was not associated with any changes in the overall safety profile of the drug. As in the double-blind phase, the most commonly reported AE was pruritus.

Data from patients exposed to OCA for over 5 years in the 201 LTSE study together with the long term safety data from other studies including the Phase 3 LTSE collectively support the

long-term safe use of OCA in patients with PBC. AEs that occurred at a frequency of ≥10% in the LTSE phase of the Phase 3 study are provided in Table 18.

Table 18: Adverse Events ≥10% During Phase 3 LTSE [N = 193]

Preferred Term, n (%)	Total OCA N=193 Patients (%)
All TEAE	182 (94)
Pruritus	111 (58)
Fatigue	34 (18)
Nasopharyngitis	28 (15)
Urinary tract infection	25 (13)
Nausea	22 (11)
Arthralgia	22 (11)
Headache	21 (11)

Data based on 120-Day Safety Data cut (29 June 2015).

6.11. Safety in Special Populations

The influence of intrinsic factors including age, sex, and BMI did not indicate any obvious differences or trends across the safety profile of these subgroups.

7. BENEFITS AND RISKS

7.1. Condition

PBC is a slowly progressing but serious, life-threatening, cholestatic liver disease that has only two treatment options: UDCA therapy and liver transplant.

7.2. Benefits

The benefits of once daily administration of OCA 5 mg and 10 mg include clinically meaningful and statistically significant improvements in ALP and total bilirubin. Effects on markers of fibrosis and markers of inflammation and immune status further support a disease modifying effect of OCA.

Once daily administration of OCA 5 mg and 10 mg resulted in clinically meaningful and statistically significant improvements in ALP and total bilirubin. These analytes have been shown to be correlated with disease progression, and when assessed over the first year of follow up, with or without therapy, are highly predictive of long-term clinical outcomes (Beuers 2011, Lammers 2014).

The majority of the benefit can be expected within the initial months of therapy and achieved when OCA is added to UDCA or as a monotherapy for patients who are unable to tolerate UDCA. In addition, OCA was effective in subpopulations at higher risk of liver transplant or death such as patients who were diagnosed at a younger age and males and those with elevated bilirubin levels.

The UK-PBC model is a tool for assessing the risk of transplant or liver-related death in patients with PBC. Studies evaluating the model support the notion that lower ALP is associated with reduced risk of clinical outcomes across a wide spectrum of disease severity based on a number of objective laboratory measures (Carbone 2015).

Clinical response of OCA can be monitored early and non-invasively via routine clinical lab assessments. The majority of improvements in ALP and total bilirubin would be expected to be observed within the initial 3 months.

Based on durability data and long-term safety data, OCA can be used chronically.

7.3. Risks and Risk Management

OCA has been used safely in PBC patients treated with OCA for up to 5 years. The most common AE, pruritus, was dose dependent but manageable using the recommended dosing regimen of 5 mg titrating up to 10 mg. Other safety observations were related to a limited decrease in HDLc. A minority of patients experienced liver-related AEs and elevations in liver biochemistries during treatment with OCA.

The AEs that are associated with OCA treatment in patients with PBC are predictable either because they are common symptoms in the PBC population (such as pruritus), are associated with downstream FXR signaling (such as a decrease in cholesterol rich HDL) or are due to its properties as a bile acid (such as local toxicities resulting in elevations in liver biochemistry).

Pruritus was manageable either with therapeutic interventions such as bile acid sequestrants or with treatment interruption and alternate day dosing. The most successful management approach for pruritus was titrating from 5 mg to 10 mg after 6 months based on patient tolerability and biochemical response instead of starting at 10 mg. Patient-reported pruritus severity, although variable, was very similar in the titration and placebo treatment groups.

Biochemical changes such as those observed in lipid levels and liver biochemistries are easily monitored through periodic testing and baseline levels should be determined prior to initiating treatment. Lipid management guidelines should be employed where appropriate and per the clinical judgement of treating physicians. To minimize the risk for hepatic toxicity, patients with hepatic impairment should initiate treatment at lower doses and with a lower frequency (5 mg weekly increasing to 5 mg twice weekly and further to 5 mg every other day) depending on tolerability and clinical response.

8. CONCLUSIONS

OCA presents a novel, new therapy with unique actions that work in addition to UDCA. Based on OCA's FXR-related mechanisms of action, the drug appears to offer a new treatment for patients that have seen no therapeutic advances for nearly 25 years.

The Global PBC study group demonstrated that patients failing UDCA treatment are at higher risk of liver transplant or death. In the pivotal Phase 3 study, despite being on a stable regimen of UDCA, ALP and total bilirubin values continued to worsen on an individual basis in placebo-treated patients. The majority of patients with PBC who are treated with OCA can expect clinically meaningful (and in some instances substantial) improvements in ALP and total bilirubin. These benefits are particularly notable as up to 50% of patients with PBC have a suboptimal response to the standard of care UDCA. Improvements in ALP and total bilirubin have been demonstrated to lead to improved clinical outcomes including transplant-free survival.

Long-term follow-up data of OCA treatment in patients with PBC over several years indicate an overall favorable safety profile. The main toxicity finding (hepatobiliary effects) in nonclinical species is predictive of toxicity in human populations at similar therapeutic margins. In patients with PBC, increases in AST, ALT, or conjugated bilirubin were generally not seen at the intended clinical doses of 5 mg or 10 mg and this risk is manageable.

Taken together, the data support an overall favorable benefit-risk profile of OCA therapy in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

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